pp. 831–938] October, 1948

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VOL. 45] 1948 [No. 10

MAIN CONTENTS :

	PAGES
Exo-Erythrocytic Schizogony in Malaria	831–844
Summary of Recent Abstracts. VIII. Typhus Group of Fevers	844–855
Rabies	855
Malaria	855–873
Blackwater Fever	873
Trypanosomiasis	873–881
Leishmaniasis	881–885
Fevers of the Typhus Group	885–893
Bartonellosis	893–894
Yellow Fever	894–895
Dengue and Allied Fevers	895
Plague	896
Cholera	896–902
Amoebiasis and Intestinal Protozoal Infections	902–909
Relapsing Fever and other Spirochaetoses	909–910
Yaws	910–911
Leprosy	911–912
Helminthiasis	912–923
Sprue	923–924
Haematology	924–927
Venoms and Antivenenes	927–928
Dermatology and Fungus Diseases	928–930
Heat Stroke and Allied Conditions	930–931
Miscellaneous Diseases	931–932
Protozoology : General	932–933
Entomology and Insecticides : General	933–936
Laboratory Procedures	936–937
Reports, Surveys and Miscellaneous Papers	937
Book Review	937–938

For detailed Contents see pp. ii, iv, vi, viii, x and xii

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EXO-ERYTHROCYTIC SCHIZOGONY IN MALARIA

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Malaria parasites* undergo four cycles of development: (1) the sexual cycle starting with the growth of gametocytes in the vertebrate host and continuing with sporogony in the tissues of the mosquito; (2) the pre-erythrocytic development of the sporozoite; (3) asexual schizogony in the red blood corpuscles and (4) exo-erythrocytic schizogony. The second and fourth stages represent the tissue phases of malaria in the vertebrate host and are the subject of this article. They are still imperfectly differentiated one from another and it is impossible, in many instances, to state where one ends and the other begins. Both phases were unknown until comparatively recently, though GRASSI (1900) in the primary wave of malaria research was forced to the conclusion that there was a third developmental cycle in the body of man, during the incubation period, and that this form would exhibit a special character of its own. He abandoned this opinion when SCHAUDINN apparently demonstrated the direct entry of the sporozoite into the red blood cell.

The theory received little attention for 30 years. JAMES (1931) revived it in order to explain many anomalies in the behaviour of the malaria parasites. He suggested that sporozoites entered connective tissue cells or cells lining the capillary blood vessels and remained there until the cells broke down, 8–10 months later, at the end of the protracted incubation period. RUGE (1936) developed the hypothesis a little further and it was eventually so well supported by accumulating knowledge that there was nearly enough indirect evidence to prove the existence of a tissue phase in human malaria. The evidence included the following points:—

1. The chromatin of the sporozoite nucleus is arranged so differently from that of the blood forms that GRASSI (1900) thought that direct development, one from the other, was impossible.

2. Most observers were unable to see the direct penetration of a red blood cell by the sporozoite. [Is there any malariologist who has not attempted to watch this process under the microscope?]

* The use of the term malaria parasites in this article is confined to blood protozoa belonging to the family Plasmodiidae. Recent work has indicated that some modification will be necessary in the definition of the families and genera in the sub-order Haemosporidiidea, and in order to show clearly their relationships a brief account of exo-erythrocytic schizogony in the various genera of the sub-order is included.

3. Quinine has little or no therapeutic action during the incubation period and yet it has a powerful action on the parasites directly they appear in the blood (SERGENT and SERGENT, 1922).

4. The experiments of FAIRLEY (1945) crystallized the exact nature of the problem. These showed that sporozoites circulated in the blood for about half an hour after inoculation and that they then disappeared. The blood was shown to be non-infectious after this half-hour until the end of the incubation period. During this interval in avian malaria (1–72 hours in the case of *P. cathemerium*), WARREN and COGGESHALL (1937) had already demonstrated that the circulating blood was non-infectious, the parasites being held in the spleen, liver and bone marrow.

Exactly who first saw exo-erythrocytic parasites in malaria will probably never be known. Among the earliest were MACCALLUM (1898), ANSCHUTZ (1910), BEN-HAREL (1923), and UEGAKI (1930); then HUFF & BLOOM (1935). But the first person to have recognized their significance appears to have been RAFFAELE (1934). He described unpigmented forms in *P. elongatum* infections and suggested (1936a) that the sporozoites of this species developed within endothelial cells. He also found (1936b) extremely scarce exo-erythrocytic parasites in *P. relictum* infections in the reticulo-endothelial cells of the liver, spleen and bone marrow of canaries, after inoculation with large doses of sporozoites.

The full significance of these findings was not realized at the time and even after 1937, when JAMES and TATE announced the discovery of the highly characteristic E.E. forms in *P. gallinaceum*, not a few (*e.g.*, HEGNER and WOLFSON, 1938a) thought these unpigmented parasites were as likely to be *Toxoplasma* as a stage in the development of *Plasmodium*. Confirmation of JAMES and TATE's work, however, rapidly followed, *P. gallinaceum* proving itself an ideal parasite for the elucidation of the whole cycle in avian malaria. The discovery of pre-erythrocytic forms in the incubation period was announced independently in 1940 by Lily MUDROW and by SHORTT, MENON and IYER, and in 1944 HUFF and COULSTON worked out the full cycle of *P. gallinaceum* in the greatest detail, whilst MUDROW and REICHENOW investigated *P. praecox* (=*relictum*).

Similar stages were seen in many other avian malarial parasites. In 1944 exo-erythrocytic schizogony in saurian malaria was described by THOMPSON and HUFF. Finally, in 1948 the tissue phase in mammalian malaria was discovered, first in the monkey parasite, *P. cynomolgi* (SHORTT and GARNHAM), and slightly later in the human, *P. vivax* (SHORTT, GARNHAM, COVELL and SHUTE).

Very useful summaries of the subject have been made by GIOVANNOLA (1939), PORTER and HUFF (1940), HEWITT (1940b) and HUFF (1947).

Terminology.

New knowledge of the life cycle of the malarial parasites inevitably required an extension of nomenclature. Definitions of the new terms are given below:—

Pre-erythrocytic schizogony.—This term refers to the development of the sporozoite during the incubation period. It may occupy one generation only, as in mammalian malaria, or several generations, as in the avian form. This stage can be said to terminate on the first appearance of parasites in the red blood corpuscles.

Exo-erythrocytic schizogony.—This was the original term employed by JAMES and TATE (1938) to describe the developmental forms they observed in the brain and other organs of chicks infected with *P. gallinaceum*. It was used indiscriminately for early and late forms. It is desirable to confine the use of

the name to stages seen in the post-patent period, *i.e.*, after the parasites have reached the blood.

Tissue Phase.—This term embraces both pre-erythrocytic and exo-erythrocytic schizogony and is to be used for preference when the exact stage of the infection is unknown.

Phanerozoite.—Any exo-erythrocytic parasite except pre-erythrocytic forms (HUFF and COULSTON, 1946).

Exo-erythrocytic schizogony : *gallinaceum*-type and *elongatum*-type. PORTER (1942) made a useful distinction between two types of schizogony. E.E. development of *gallinaceum*-type occurs predominantly in the lymphoid-macrophage system, including endothelium. E.E. development of *elongatum*-type is confined to the wandering cells of the blood and organs (particularly the haemopoietic system).

Cryptozoite.—HUFF, COULSTON and CANTRELL (1943) devised this word to denote the first stages in the development of the sporozoite. Cryptozoites are the product of the first division of the sporozoite and are contained in a cryptozoic schizont.

Metacryptozoite.—Following the first cryptozoic generation, are schizonts which produce metacryptozoites and the term (proposed by HUFF and COULSTON, 1944) includes all pre-erythrocytic stages with the exception of cryptozoites.

Micromerozoite.—Certain E.E. schizonts consist of many nuclei and little cytoplasm. These microschizonts eventually produce a large number of micromerozoites (128 or more in the case of *P. relictum*, REICHENOW and MUDROW, 1943). In size and structure they are like the merozoites resulting from schizogony in red blood corpuscles and they are destined to enter such cells themselves.

Macromerozoite.—The macromerozoites are larger bodies than the micromerozoites ; they probably number not more than 64 (in *P. relictum*) within the macroschizont. They do not invade red blood corpuscles, but enter tissue cells.

Megaloschizont.—This term was applied by HUFF (1942) to describe the large schizonts of *Leucocytozoon* in the tissue cells of the heart, spleen, intestine and liver. The mature forms measure over 100μ in length and contain thousands of merozoites. They are solid bodies.

Merocyst.—An analogous structure to the megaloschizont is the merocyst (GARNHAM, 1947) of *Hepatocystes kochi*. During the exo-erythrocytic development of this parasite the substance of the schizont becomes highly vacuolated. The vacuoles coalesce in a large internal space and this space is bounded by a thick wall containing innumerable merozoites. The merocyst measures about 2 mm. in diameter.

Cytomere.—WENYON (1926) defines cytomeres as the intermediate bodies of a schizont which actually produce the merozoites. When a certain number of nuclei have formed, the schizont divides into the same number of individual masses, each with a single nucleus. These are the cytomeres ; their nuclei undergo further division, and finally merozoites are budded from their surfaces. Such a clear-cut process is rarely seen in the Haemosporidiidea but various observers have noted the partial differentiation of the schizont during its growth into separate islands or cytomeres. ARAGÃO (1908) first described the phenomenon in *Haemoproteus*. JAMES and TATE (1938) stated that during the growth of *P. gallinaceum* schizonts, the cytoplasm breaks up into a number of cytomeres on the periphery of which the merozoites are developed on digitiform processes. HUFF (1942) showed that during the formation of the megaloschizont of *Leucocytozoon*, the body became divided into numerous (usually several

hundred) individual cytomeres; later multiplication of the nuclei being followed by a loss of such differentiation.

Schizont.—This familiar term has been defined by the Malaria Commission of the League of Nations (1940) in the following manner: "Intracellular asexual form in any stage (strict usage). Restricted in practice to designate asexual forms other than ring forms. There may be distinguished young schizonts with undivided chromatin, medium forms with two or more chromatin masses and mature (or adult) schizonts with the chromatin fully divided. When chromatin has fully divided with formation of merozoites, the schizont is known as an adult schizont (sporulation form, segmentation form, rosette)."

The Tissue Phase

Avian Parasites

The avian parasites have been studied in considerable detail and it is beyond the scope of this article to describe more than the main features of the different species.

P. gallinaceum.—The initial development of the sporozoite of this parasite was observed by HUFF and COULSTON (1944). Sporozoites remain within the intracellular spaces up to six hours after inoculation. They then, or earlier, enter cells of the lymphoid-macrophage system of the skin. The cryptozoites take about 42 hours to reach maturity. On first entry into the host cell, the sporozoite assumes an oval or spheroidal shape. By about 24 hours, the nucleus divides into two fragments; the nuclei rapidly increase in number to over 100. Finally a peripheral layer of elongate merozoites is produced on the surface of the dense unsegmented core of the parasite. Each cryptozoite resembles a sporozoite except that it is shorter. The schizont ruptures and the cryptozoites enter adjacent cells of similar type. These primary forms occur also in the spleen and in other organs.

The metacryptozoite generations which follow are, with a few exceptions, indistinguishable from the foregoing. Schizogony is completed in between 70 and 84 hours, and some of these metacryptozoites may enter erythrocytes. These forms are very numerous in the site of inoculation, and in the spleen, heart, kidney and brain (in this order) after intravenous inoculation of sporozoites.

Two types of schizonts may be distinguished even as early as the fifth day. These are the macroschizonts producing 100–200 macromerozoites, and the microschizonts producing up to 1,000 tightly packed, deeply staining micromerozoites.

Other methods of demonstrating pre-erythrocytic forms have been utilized. GORDON and HANCOX (1947) inoculated suspensions of sporozoites free of bacteria directly into the brain and observed parasites much like the above. This method demonstrates well the peripheral arrangement of the nuclei in the growing schizont.

There appears to be no major distinction between the metacryptozoic schizonts of the pre-erythrocytic cycle and the exo-erythrocytic forms originally described by JAMES and TATE (1938). The latter forms, however, come from two sources, directly from the metacryptozoites and indirectly from asexual forms in the blood. DOWNS (1947) proved that a single trophozoite was capable of producing infections in the chick in which typical exo-erythrocytic schizogony followed. The exact line of descent of individual schizonts in the late stage is usually untraceable; the best description is probably that of DAVEY (1944) who represented the process diagrammatically in the following way (slightly modified):—

Sporozoites → primary tissue phase → secondary tissue phase
↓ ↑
blood phase

In a fully developed infection, the development of the schizonts proceeds as follows. The youngest stages are small ovoid bodies with a single large irregularly-shaped mass of chromatin. As the parasite grows, the chromatin divides into many triangular masses. Cytomere formation follows and eventually merozoites are produced, each merozoite possessing an angular or anvil-shaped mass of chromatin with a scarcely discernible amount of cytoplasm. The chromatin is of a peculiar diffuse texture; it was shown by UNGO-MUGDAN (1938) to contain a large quantity of thymo-nucleic acid. The size of the schizont appears to be limited only by the type of host cell invaded. Great elongated masses containing hundreds of merozoites may be seen within a capillary, though it is difficult to be certain whether such masses comprise single schizonts or many. Macro- and micro-schizonts are encountered. A feature common to all E.E. schizonts is the absence of pigment; this is because the parasites are in cells devoid of haemoglobin.

The localization of these forms within the body has been described by BRUMPT (1937) and JAMES and TATE (1938) and, more recently, by TULLIS (1947). Brumpt places the infected organs in the following order in respect of the comparative abundance of E.E. schizonts: brain, spleen, lung, myocardium, kidney, liver and bone-marrow, though he admits that with the exception of the brain, the distribution in the organs varies very much from bird to bird. The brain is an especially important focus of development and the schizonts ultimately come to occlude most of the capillaries in this organ. Infection of leucocytes in the peripheral circulation rarely occurs. Tullis showed that after the intravenous inoculation of blood containing *P. gallinaceum*, small numbers of E.E. schizonts appeared on the fourth day in R.E. cells of the blood and of the spleen, and on the sixth day in the liver, heart, lungs and intestine. They are rarely found later in the pancreas, fat, kidney, bone-marrow and striated muscle. Other uncommon sites are adrenals, ovaries and thymus.

Many tissue cells appear to offer facilities for E.E. development but all appear to belong to the reticulo-endothelial system. The sporozoites first enter macrophages and polyblasts of the skin. The macrophages may be of either fixed (histogeneous) or wandering (haematogeneous) origin. In the spleen, the parasites enter endothelial and reticular cells lining the small arterioles and capillaries. In the later stages of an infection, development occurs chiefly in the fixed cells of the R.E. system such as the endothelial cells of capillaries, Kupffer cells of the liver, and reticulo-endothelial cells lining the venous sinuses of the lungs, spleen and bone-marrow. E.E. schizonts are occasionally found in circulating leucocytes or in heterophil granulocytes in the subcutaneous tissue. In such instances, the parasite has apparently entered the host cell by accident and development probably is not completed.

P. relictum.—The pre-erythrocytic stages of this parasite bear a close resemblance to those of *P. gallinaceum* and have been studied in detail by COULSTON and HUFF (1947). Development occurs in the cells of the lymphoid-macrophage system and in fibroblasts. The cryptozoic schizont of *P. relictum* is little more than half the size of the corresponding structure in *P. gallinaceum* (5 or 6 μ as compared with 10 μ), and the number of merozoites is only one half or one third of the number in *P. gallinaceum*. The cryptozoites are more ovoid or bluntly elongate instead of sharply pointed and crescent shaped. The difference in size between the two species persists in the metacryptozoic generations. Macro- and micro-schizonts have been observed by REICHENOW and MUDROW (1943). RAFFAELE (1936) described the later stages from the liver, spleen and bone-marrow of infected canaries. The schizonts measure 18–20 μ in diameter and contain 40 nuclei. The cytoplasm is alveolar but not vacuolated. RODHAIN (1938) made further observations on this infection in penguins. The E.E. forms were most numerous in the lungs and liver but also

occurred rarely in the brain. Multiple infections of cells were seen. FANTHAM & PORTER (1944) also found scanty E.E. forms in penguin malaria, which they described under the name of *P. relictum* var. *spheniscidae*. MANWELL (1940) studied a variety of this parasite, *viz. P. relictum* var. *matutinum*, in canaries. Localization in the brain was common and the presence of large and conspicuous vacuoles in the schizonts was a constant peculiarity in this variety. In tissue culture, HAWKING (1946) noted that the merozoites were elongate and sometimes arranged radially around a central core.

MISSIROLI's (1940) account of the development of the sporozoite of *P. relictum* differs from that of the American workers, particularly in regard to the primary place of development which Missiroli states is extracellular, resulting in the formation of four merozoites. These merozoites are said to enter red blood corpuscles and start the blood cycle.

P. cathemerium.—This avian parasite is very similar in morphology, in all forms, to *P. relictum*. Its common E.E. sites are the brain and the liver, though in heavy infections unpigmented schizonts may be found in the peripheral blood (in eosinophiles). The early forms have been described by KIKUTH and MUDROW (1938 and 1939) and were shown to begin as uninucleate parasites lying in endothelial cells or monocytes ; these parasites later underwent schizogony, dividing into at least 11 merozoites. The late stages have been described incompletely by many authors—HEGNER and WOLFSON (1938a) illustrated what were certainly the E.E. schizonts of this parasite, though at that time they were not prepared to differentiate them from *Toxoplasma*. In length they may measure 32μ and there may be 100 or more merozoites.

P. circumflexum.—This large parasite, of the elongate gametocyte group, has been studied by MANWELL and GOLDSTEIN (1939). E.E. schizonts are found in the following organs (in order of frequency)—lungs, brain, spleen, liver, bone marrow, heart and ovaries. The schizonts reach the size of 32μ in diameter and the merozoites number at least 170. A characteristic feature is the elongate character of the merozoite. The schizonts sometimes show one or more vacuoles, and two kinds occur, one with lightly-staining, and the other with much more heavily-staining cytoplasm. They invade the endothelial cells of the cerebral capillaries and the monocytes of other organs. Pre-erythrocytic stages are unknown.

P. lophurae.—The pre-erythrocytic cycle of *P. lophurae* has been studied by HUFF, COULSTON, LAIRD and PORTER (1947). Unfortunately, the host birds employed by these workers did not appear to be completely suitable for the parasite and many of the E.E. parasites were in an abnormal or degenerate condition. They occur in cells of the lymphoid-macrophage system and in fibroblasts and, so far, they have only been recovered from the site of inoculation of the sporozoites in the skin. No constant differences were observed between these pre-erythrocytic forms and those of *P. gallinaceum*. In the later stages, exo-erythrocytic parasites are abundant in the capillaries of the brain. Macro- and micro-merozoites were observed by TONKIN and HAWKING (1947) in infected turkeys.

P. durae.—PURCHASE (1942) and SIMPSON (1944) reported exo-erythrocytic schizogony in this parasite of turkeys. The forms are most numerous in the lungs and brain but also occur in the liver and spleen. In the brain, infection is so intense that the capillaries are completely occluded. The exact morphology of these parasites remains undescribed and the pre-erythrocytic stages are unknown.

Avian Plasmodia of Small Size.—The malarial parasites of birds are conveniently classified into larger and smaller species (RUSSELL, WEST and MANWELL, 1946). Exo-erythrocytic schizogony has been found in few of the smaller species, probably because the infections have not been sufficiently

studied. BARRETTO (1943) has described, briefly, tissue forms in *P. juxtanucleare*. He found them solely in the brain capillaries. The schizonts were elongated structures with 2–19 blocks of chromatin. HEGNER and WOLFSON (1938b) described schizonts in reticulo-endothelial cells from birds infected with *P. nucleophilum*. These infections were apparently mixed with *P. cathemerium* and it seems probable that the schizonts were in reality those of the latter species.

P. elongatum.—Exo-erythrocytic schizogony in this species follows a totally different course from that of the parasites described above. RAFFAELE (1934) and HUFF and BLOOM (1935) give detailed descriptions of the development of this species ; they demonstrated that schizogony occurred in a wide variety of cells, extending from mature erythrocytes to erythroblasts, haemocytoblasts, plasma cells, macrophages and granulocytes. The overwhelming majority of the parasites occur in the red blood cell series, probably less than 10 per cent. in other cells. Except for (*a*) size and number of merozoites and (*b*) presence or absence of pigment, there appears to be little difference in the character of the schizont whatever cell it may be inhabiting. The essential difference between *P. elongatum* and the other parasites is the fact that exo-erythrocytic stages of the latter are largely confined to fixed tissue cells, while these stages in *P. elongatum* occur only in wandering cells.

The schizonts of this parasite produce 4–30 elongated merozoites which are arranged in a most characteristic fashion, more like the arrangement seen in schizogony in haemogregarines than in plasmodia. They lie in parallel rows or bundles. Pigment is produced only in the polychromatophil erythroblasts, normoblasts and erythrocytes. In the erythroblasts only a small granule of pigment is produced. There exists, therefore, no clear line of differentiation between exo-erythrocytic and erythrocytic schizogony in this species, and even when the former can be distinguished, it presents features which link it closely with the ordinary schizogony of the blood. Thus, the number of merozoites is small, the cycle of development is short (24 hours), there is no differentiation into macro- and micro-schizonts and, finally, there is the absence of any tendency to invade fixed lymphoid-macrophage tissue.

The complete pre-erythrocytic cycle is still to be described. RAFFAELE (1934) found exo-erythrocytic parasites early in infections before invasion of the peripheral blood had begun and he assumed from this that pre-erythrocytic development occurred in endothelial cells.

Saurian Parasites

Exo-erythrocytic schizogony in American lizards was discovered by THOMPSON and HUFF (1944). It has also been observed by the present reviewer (unpublished work) in the East African skink, *Mabuia maculilabris*.

The cycle in *P. mexicanum* is of considerable interest in that it occurs in both wandering and fixed tissue cells ; in other words, it partakes of the characters of both the *gallinaceum*- and the *elongatum*-types of schizogony. The parasites invade basophil erythroblasts, lymphocytes, monocytes, thrombocytes and granulocytes and in such cells the round or oval schizonts produce elongate merozoites, 10 to 40 or more in number. The *gallinaceum*-type of schizogony is seen in reticular cells, endothelial cells of capillaries, littoral cells of the liver and macrophages. There is a strong tendency to invade the true endothelium. In these situations, the schizonts are larger and contain 72 or more round merozoites.

Mammalian Parasites

Reports claiming the discovery of exo-erythrocytic schizogony in human or monkey malaria have appeared from time to time and there can scarcely be a single worker in this field who has not thought at one time or another that he

has at last found the cryptic forms. Usually, on reflection and re-examination, it has been possible to find an alternative explanation, but some claims were put forward and their unreliability has recently been analysed by ANGELINI (1947). Other workers have described various intracellular bodies, but have regarded them more conservatively (*e.g.*, DECOURT and SCHNEIDER, 1938; DUBIN, 1947). When the liver schizonts of *P. cynomolgi* were ultimately discovered (SHORTT, GARNHAM and MALAMOS, 1948) their morphology was so entirely unequivocal that they received instant acceptance and the long search at last came to an end. So far, the exo-erythrocytic forms have only been demonstrated in *P. cynomolgi* and *P. vivax*. Recent discoveries in other mammals refer to parasites incorrectly placed in the family Plasmodiidae; they are mentioned briefly later in this article.

The technique leading to the discovery of these forms was as follows. In the monkey it involved the introduction of hundreds of thousands of sporozoites by bite and by the inoculation either of large numbers of the whole mosquitoes intraperitoneally, or of the salivary glands intravenously. Seven days later, the animal was sacrificed and specimens were taken from every organ and tissue. Sections were stained and examined and the schizonts were eventually found in the liver material. After this, it was an easy matter to repeat the experiment in man with *P. vivax* and to extract the necessary tissue by liver biopsy.

P. cynomolgi.—Pre-erythrocytic schizogony of this species has been described by SHORTT and GARNHAM (1948b) and by HAWKING, PERRY and THURSTON (1948). The process takes place in the parenchymatous cells of the liver and probably only one generation is involved. The earliest forms were seen on the fifth day after infection. They are spherical or ovoid bodies about 10μ across and contain about 50 pieces of irregularly shaped chromatin lying throughout the granular cytoplasm. A characteristic of this stage is the very sharply cut margin of the parasite. Growth continues and maturity is reached about the eighth or ninth day. During this time, a few curious vacuoles develop in the parasite and indentations of the periphery occur, sometimes resulting in the formation of one or more lobose arms. Nuclear multiplication continues and eventually nearly a thousand merozoites are formed. Each merozoite consists of a small fragment of chromatin on one side and a fairly dense piece of cytoplasm on the other, giving the appearance of a "solid ring" a little over 1μ in diameter. The mature schizont itself measures about 35μ in diameter. Exceptionally, forms as large as 60μ are to be seen.

After the rupture of the schizont and the escape of the merozoites into the sinusoids, invasion of the residual mass by phagocytes occurs. These cells are lymphoid-macrophage cells, plasma cells and polymorphonuclear leucocytes.

Persistence of the tissue cycle in the liver parenchyma has recently been demonstrated by SHORTT and GARNHAM (1948c). Schizonts were found 3½ months after the original sporozoite-induced infection and after a month's latency, when parasites were absent from the peripheral blood. Schizonts were extremely rare; they resembled pre-erythrocytic forms in most respects, a possible difference being that the younger (5-day-old) parasites appeared to possess a well defined, wavy, limiting membrane. There is little doubt that these schizonts represent the relapse forms. They presumably continue to develop in the liver throughout an infection, producing showers of merozoites which, however, are normally destroyed by the immune mechanism. Something upsets immunity; the merozoites are then able to continue the erythrocytic cycle and a relapse ensues.

P. vivax.—The E.E. schizonts of this species resemble those of *P. cynomolgi* very closely. Ovoid plasmodial masses develop within the parenchymatous cells of the liver. These exhibit vacuoles, indentations of periphery and

nuclear multiplication, resulting in the formation by the seventh day of a fully mature schizont with 800–1,000 merozoites. The size of the schizont is, perhaps, rather larger than in *P. cynomolgi*, about 42 μ in diameter.

Exo-erythrocytic Schizogony in the Haemoproteidae

The following genera are recognized in this family, *Haemoproteus*, *Leucocytozoon* and *Hepatocystes*. It is probable that the family will have to be widened to include the malarial parasites of the bat, flying fox, sitatunga and other mammals; these also are considered briefly in this section. All the members of this family exhibit gametocytes only in the blood stream. The Haemoproteidae show affinities not only with the Plasmodiidae but with various genera in the Theileriidae. "Koch's blue bodies" of *Theileria parva* bear a strong resemblance to the E.E. forms of avian plasmodia and halteridia, and the cycle of the newly described piroplasm, *Cytauxzoon sylvicaprae* Neitz and Thomas (1948) of the Duiker shows an even closer relationship.

Haemoproteus was shown by Aragão (1908) to undergo a tissue phase in the endothelial cells of the blood vessels of the lungs and other organs of the body. Segmentation into cytomeres occurs, each of these continues to grow and eventually enormous numbers of merozoites are produced, enclosed by fine cyst walls. These forms reach 60 μ in diameter, and smears show that the cytoplasm has a meshed structure with fairly numerous vacuoles and many nuclei. Wenyon (1926) noted that cytomere formation was not inevitable but that the schizont—a large sausage-shaped body—might give rise directly to merozoites. These schizonts may collect in groups in the organs, *e.g.*, liver or spleen, separated from each other by walls of indeterminate origin, the whole focus measuring several hundred microns in diameter.

Leucocytozoon E.E. schizonts were described by Huff (1942). Two types were found, one occurring in parenchymatous cells of the liver, causing little alteration in the cell, and the second, the megalo-schizont, in the heart, liver, spleen and intestine. The megalo-schizonts are formed from numerous cytomeres which eventually give rise to extremely numerous bacilloid merozoites, arranged without order in the schizont. These forms may be as long as 105 μ. It is probable that the megalo-schizont develops within macrophages and also in cardiac muscle cells. These cells become enormously hypertrophied and the nuclei also enlarge.

Hepatocystes kochi (a parasite of the lower African monkeys) has recently been studied by Garnham (1948) and details of its exo-erythrocytic cycle were elucidated. Development proceeds in the parenchymatous cells of the liver, first as a minute round body, then as a sphere with peripheral nuclei; the nuclei later multiply and become scattered throughout the cytoplasm. The surface of the parasite shows multiple invaginations; vacuolation occurs and the fluid accumulates in a large central vacuole which expands to form the merocyst. Further division of the nuclei has continued in the meantime, possibly with the formation of cytomeres. Eventually the merozoites collect in enormous numbers in the wall of the merocyst, which ruptures and the majority of the merozoites escape into the circulation where they grow into gametocytes. The mature merocyst measures up to 2 mm. in diameter. These E.E. forms persist throughout the infection, discharging a stream of gametocytes into the blood.

A similar parasite has recently been described by Ray (1948) from the Himalayan flying-squirrel. It has an E.E. cycle in the liver resembling in many ways that of *H. kochi*, though the cysts are multiple.

Malarial Parasites of Bats.—Mer and Goldblum (1947) found that the bats (*Myotis myotis* and other species) of Palestine, harboured a blood parasite which underwent intense schizogony in the reticular cells and the granulocytes of the

bone-marrow. E.E. forms were also present in the wandering and fixed macrophages of the lung, kidney and liver. The parasites in the liver measure little more than 6 μ in diameter. They are, of course, unpigmented and they produce a relatively small number of merozoites. Ectoparasites of the family Nycteribiidae infest these bats and it is claimed that the glands of one fly contained sporozoites.

Another interesting parasite of bats (the fruit bat—*Pteropus gouldi*) was studied by MANWELL (1946) in New Guinea. In addition to gametocytes, he found a fair number of unpigmented schizonts in the peripheral blood and these schizonts were all extracellular. They contained a variable number of merozoites and were said to resemble the E.E. forms of avian malaria. It is possible that these bodies in reality were detached portions of a rupturing merocyst. They are not unlike the structures which SCHWETZ (1933) described from the peripheral blood and bone-marrow in *H. kochi* infections. It is doubtful whether they should be regarded as the mammalian equivalent of *P. elongatum* because, although in the blood, they lie free and are not in cells of the haemopoietic system.

Biological Significance of E.E. Schizogony

The conclusion that E.E. schizogony was an essential part of the life cycle of malaria parasites was accepted by most workers after the early work of James and others. Because of its erratic and cryptic nature, however, some people at first were unwilling to accept this interpretation and they put forward several others. BRUMPT (1937) suggested that the phenomenon might represent an accidental histotropism caused by the unfavourable action of the blood on certain merozoites escaping from the ordinary blood schizonts. CHORTIS (1938) thought that E.E. schizogony was not a normal developmental stage but appeared as the result of a loss of function of the reticulo-endothelial cells. These cells start phagocytosis of the parasites but are unable to complete the process and the parasites then continue their own development. CORRADETTI, as late as 1941, regarded the presence of E.E. forms as a sort of accident in the life history of malarial parasites, occurring in only a few species ; he also thought that development in histiocytes was not undergone by sporozoites. The same worker (1942) stated that the extent of the process depended upon the degree of balance between host and parasite—in other words, upon immunity. His experiments had shown that when sporozoites or suspensions of tissues containing E.E. forms were inoculated into clean birds, E.E. forms readily appeared—because there was no immunity ; if, however, the inoculation was made into birds in the latent phase of a homologous infection, no E.E. forms appeared.

Further knowledge, particularly in regard to the tissue phase in mammalian malaria, has made it clear that exo-erythrocytic schizogony is a fundamental part of the cycle of probably all the malaria parasites, just as it is in other members of the Haemosporidiidea. Variations in incidence occur, but these are no greater than similar fluctuations in the number, for instance, of gametocytes, and as is well known, certain strains of parasites can become completely and permanently gametocyte-free. It is now clear that the sporozoite on inoculation proceeds to a certain site, the exact location of which depends upon the species, and there develops through one or more generations into a schizont which produces blood infecting merozoites. Tissue forms may persist in this original site or elsewhere in the body, or they may be so evanescent that after the incubation period, they disappear entirely. With certain species, exo-erythrocytic forms may develop, as CORRADETTI (1941) and others have shown, directly from blood schizonts even from the inoculation of a single trophozoite.

HAWKING *et al.* (1948) go as far as to speculate on the phylogenetic relations between the malaria parasites and allied protozoa belonging to the Eimeriidea, based on their common development in intestinal epithelium (*e.g.*, *Schellackia*) or in hepatic epithelium which is embryologically derived from the former (*e.g.*, *P. cynomolgi*, *H. kochi*).

There are still many gaps in our knowledge of E.E. schizogony. The morphology of this stage is incompletely described, although novel methods have been devised to study it. SHORTT, MENON and IYER (1940) used inoculation into the chorio-allantois of the fowl embryo to observe *P. gallinaceum* infections; HAWKING (1944) and more recently GRAMICCIA and BLACK (1948) have employed tissue culture as a means of studying E.E. forms. The behaviour also of these parasites is only partly understood. E.E. forms are present in some strains of a species and yet may be completely absent throughout hundreds of passages in another, as HEWITT (1940a) found in *P. cathemerium*. On the other hand, growth in tissue culture may produce a strain which results in infections of an exclusively exo-erythrocytic nature, this peculiarity being maintained unchanged through many subsequent passages (LEWERT, 1948). The development of E.E. stages in different hosts has been studied by HUFF, COULSTON, LAIRD and PORTER (1947); they showed that *P. lophurae* exhibited most numerous E.E. forms in young turkeys, pheasants and canaries, but few in guinea fowls; on the other hand, pre-erythrocytic forms were commonest in guinea fowls and less common and more abnormal in morphology in chickens, turkeys and ducks.

The infectivity on sub-inoculation of organs containing pre-erythrocytic parasites shows certain peculiarities which at present are not understood. In avian malaria, subinoculation is always successful; in mammalian, it never is. In this respect, the mammalian plasmodia behave like the Haemoproteidae whose asexual stages are only slightly infective (COATNEY, 1933). The failure to infect may be due to the localization of the parasites in special cells (*e.g.*, hepatic parenchyma rather than undifferentiated endothelium) or it may be because there is probably only a single and lengthy cryptozoite stage in mammalian malaria, with no free merozoites until the end of the incubation period. The chemotherapeutic action of drugs is likely to show corresponding variations based partly on this fundamental difference between the various species. A discussion on this subject is beyond the scope of the present review.

For a long time past, people have felt the need for a reclassification of the malaria parasites. MISSIROLI (1937) suggested the creation of a new genus *Istiocytozoon* for the two avian parasites *P. elongatum* and *P. gallinaceum*, based on their evolution in reticulo-endothelial cells. This has subsequently proved to be an unsatisfactory basis and the name has been unacceptable to the majority of workers. CORRADETTI (1938) took the opposite view and suggested fusing the two families Plasmodiidae and Haemoproteidae, because the distinction is a purely physiological one, referring to the type of host cell parasitized. This interpretation would appear to be invalid because there are gross morphological differences and also, as PORTER and HUFF (1940) pointed out, the two families have distinctive invertebrate hosts. The present position is well summarized by GRAMICCIA (1948) in the statement that a revision of the sub-order Haemosporidiidea is necessary but cannot be made until many obscure points in the biology and life history of the more important parasites are cleared up. In the reviewer's opinion, taxonomic changes should be postponed until the nature of the tissue phase has been elucidated in: (a) *P. falciparum* or *P. reichenowi*; (b) the small avian plasmodia (*e.g.*, *P. rouxi*); (c) the mammalian analogue of *P. elongatum* (possibly the plasmodium of the New Guinea flying fox); and (d) probably certain novelties such as the virulent haemotozoon (*P. berghei*) of the Congo tree rat (VINCKE and LIPS, 1948) and

the plasmodia of the Canadian bull frogs (FANTHAM, PORTER and RICHARDSON, 1942). *P. knowlesi* might be added to this list because of certain peculiarities, *e.g.*, its short cycle (24 hours) and its apparent non-transmissibility by mosquitoes. A basis for classification is indicated in the table below, which shows tentatively the position of the more important genera and species.

Size of E.E. Schizonts	Location of E.E. Schizogony	HAEMOPROTEIDAE: Gametocytes only in Blood Invertebrate Host not a Mosquito	PLASMODIIDAE: Gametocytes and Schizonts in Blood Invertebrate Host a Mosquito
Macroscopic or nearly so	Endothelium of blood vessels	*Haemoproteus*	+
	Liver, heart, kidney parenchyma	*Leucocytozoon*	+
	Liver parenchyma	*Hepatocystes*	*Plasmodium vivax, cynomolgi*
Microscopic	Reticulo-endothelium	*Plasmodium** sp. of Palestine bats	*Plasmodium** *gallinaceum, durae*, etc.
	Haemopoietic system	*Plasmodium** sp. of New Guinea flying fox	*Plasmodium** *elongatum*
	R.E. and haemopoietic system	+	*Plasmodium mexicanum*

* Re-classification may be required.
\+ Gaps to be filled.

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SUMMARY OF RECENT ABSTRACTS*

VIII. TYPHUS GROUP OF FEVERS

Proteus OX19 type: Vectors louse and flea

Louse typhus

Epidemiology.—STUART (p. 193) shows that louse-borne typhus and louse-borne relapsing fever can exist independently of each other, but that where they are related, the epidemic of typhus tends to appear earlier by one or more years than the epidemic of relapsing fever.

AMBERSON (p. 58) shows that louse typhus is constantly present in Egypt, and that from 1941 to 1944 and perhaps later it was epidemic, reaching a peak incidence of 229 per 100,000. In the *Bulletin de l'Office International d'Hygiène Publique* (p. 192) the point is made that during the period 1939–45 the peak incidence of typhus in Tunisia was in March–May, except for 1945 when it was in January. The claim is made that repeated mass vaccination has controlled the epidemic.

PADILLA (p. 192) shows that most of the cases of typhus in Guatemala are of the louse-borne type, but that a few flea-borne cases occur.

Aetiology.—PAYZIN (p. 703) observed that rickettsiae [presumably *R. prowazeki*] frozen and dried and sealed under hydrogen, were viable after 132 days at −14°C.

OLITZKI *et al.* (p. 195) show that *R. prowazeki* and certain other Gram-negative organisms contain a common toxic constituent. The labile toxin of *R. prowazeki* and *R. mooseri* present in the supernatant fluid after centrifugation of yolk-sac cultures, passes Seitz filters (OLITZKI and BUECHLER, p. 196).

Tests.—MEGAW (p. 300) quotes FELIX, who points out that some of the strains of *Proteus* used for tests in the Middle East during the war, had become useless by the time they reached the laboratories. Cultures dried *in vacuo* and stored

* The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1947, v. 44. References to the abstracts are given under the names of the authors quoted and the pages on which the abstracts are printed.

in ampoules are said to keep indefinitely, and can be used with confidence for making suspensions.

In a study of 1,084 strains of *Proteus* in areas free from human rickettsial diseases, WINKLE (p. 573) found 12 serological types, including 4 that behaved like *X2*, *X19*, *XU*, and *XK*. The same author (p. 574) isolated two strains of *Proteus X19*, one from the blood and one from the urine, of patients with (or suspected of) typhus.

WISHART and MALCOMSON (p. 194) show that *R. prowazeki* and *R. mooseri* possess type-specific antigens labile at 60°C., and a common antigen stable at 100°C. but destroyed at 120°C. The latter contains two factors, one of which is common to *Proteus OX19*. The Weil-Felix reaction, therefore, is a specific immunological reaction. BENDICH and CHARGAFF (p. 407) have extracted two antigenic fractions from *Proteus OX19*, one of which shows specificity with typhus sera and with *Proteus* antisera; the other with the latter only.

The Pan-American Typhus Commission (p. 703) have adopted as standard the Castañeda *Proteus OX19* antigen.

SIEVERS (p. 890) uses living *Proteus OX19* for the Weil-Felix test.

A rapid slide test for typhus, in which serum and an emulsion of *Proteus OX19* are used, is described by SANTO; readings are made within 12 minutes.

For use in agglutination tests, SHEPARD and TOPPING (p. 573) describe a method of preparing rickettsial suspensions from infected yolk sacs, which entails washing the rickettsiae, centrifugation, and absorption of much of the remaining yolk-sac material with Celite. The method was satisfactory with the rickettsiae of epidemic and murine typhus, and Rocky Mountain fever; less so with Q fever and not at all with scrub typhus.

GIROUD and JADIN (p. 891) have used the rickettsia-agglutination test with epidemic and murine antigens, in epidemic typhus. Homologous agglutination is at first no greater than heterologous, but becomes so at a later stage. HAMMARSTRÖM *et al.* (p. 194) have found the rickettsia-agglutination test more sensitive and reliable than the Weil-Felix in typhus. They describe the technique used; even the slightest microscopical clumping was regarded as positive. In tests on refugees to Sweden from German concentration camps, in whom typhus occurred, HAMMARSTRÖM *et al.* (p. 652) found that the rickettsia agglutination test gave positive results about the 5th day of disease, but the Weil-Felix only about the 9th day. The former, therefore, appears to be the more reliable in diagnosis.

PACKALÉN (p. 809) prefers the complement-fixation test to the rickettsia-agglutination test because of the difficulty of the Hammarström technique. BENGTSON (p. 302) has shown that with the complement-fixation reaction, epidemic and endemic (murine) rickettsiae can be differentiated because the reaction with homologous strains is at a higher titre than reactions with heterologous strains. She used 16 epidemic and 3 endemic strains in these tests, and the corresponding sera from convalescent guineapigs. In comment, MEGAW points out that the margin of difference is not great. MALCOMSON and WISHART (p. 407) have been able to differentiate epidemic and murine typhus by means of the complement-fixation test in which type-specific antigens are used, the titres being 2–4 times as high with homologous as with heterologous antigens. The same authors (p. 408) have written on the serology of typhus, but for details the original should be consulted.

The quantitative complement-fixation test for typhus was used experimentally by VARLEY and WEEDON (p. 654), who used various epidemic and murine antigens and guineapig antisera. Although titres were high when homologous antigens and antisera were used, there were some results which indicated that the test is not always type-specific in that one murine antiserum did not give high titres with all the murine antigens.

GIROUD and JUDE (p. 1057) have found that the complement-fixation reaction is more sensitive than the Weil-Felix in giving positive results in persons inoculated with rabbit-lung epidemic vaccine.

Clinical findings : treatment.—The clinical features observed in 244 cases of typhus in middle Europe during the war are recorded by LACHNIT (p. 704). The incubation period was never less than 12 days. The liver was usually enlarged. An early leucopenia was followed by moderate leucocytosis. In many cases there were casts and red cells in the urine.

GIROUD (p. 704) sets out the reasons why he thinks that inapparent and latent infections play a part in the epidemiology of typhus, and gives examples of the isolation of rickettsiae from apparently healthy persons. He regards the rickettsia-agglutination test as more reliable than the Weil-Felix. JUDE and BRUMPT (p. 811) report two cases in which injection of gonococcus vaccine apparently lighted up latent typhus infections which had probably been present for some time. They suggest that such latent infection may play a part in the carry-over of infection from one epidemic to another.

HEIDE (p. 193) claims to have demonstrated rickettsiae in blood smears of patients with louse-borne typhus.

NORVIIT (p. 653) states that electrocardiographic readings show abnormalities in most cases of typhus, but thinks that extracardiac factors must play an important part in producing them.

VAN DEN ENDE *et al.* (p. 472) have written a substantial monograph on chemotherapeutic and other studies of typhus, in which they describe tests on 238 substances in animals, and trials in man of the two most favourable compounds. The results in man were not encouraging. The monograph also contains chapters on vaccine preparation (murine type in mouse lungs) and on the antigenic structure of epidemic and murine rickettsiae. These differ sufficiently to be regarded as distinct species, but they contain antigens which are heat-labile and which are not specific, as well as those which are specific.

HAAGN (p. 892) strongly believes that full doses of strophanthin, and of intravenous calcium, given as early as possible, are of great value in typhus.

MORGAN *et al.* (p. 808) show that streptomycin has only slight inhibitory effect when administered into yolk sacs of embryo chicks shortly before inoculation with *R. prowazeki*, less with *R. mooseri*, and none with *R. orientalis*. They think that it is unlikely to be useful in these rickettsial infections of man.

Vaccination.—PSHENICHNOV and RAIKHER (p. 655) have devised a new method of preparing the Weigl vaccine, which involves feeding lice on a mixture of defibrinated blood and triturated bodies of infected lice, through a membrane of skin from fresh human cadavers.

CABASSO (p. 809), having shown that guineapig blood is not toxic for human lice (as is generally thought) but that lice cannot digest it, points out that they may be fed on guineapigs infected with *R. prowazeki*, and subsequently on immune human beings, and that they thus develop massive infection. This method of infecting lice has advantages over the Weigl rectal method. WEIGL (p. 1058) has found, during the war in Poland, that the louse-intestine vaccine was much more effective than the mouse-lung and yolk-sac vaccines. He thinks that *R. prowazeki* maintained in mice steadily approaches the murine type, and that vaccines of murine type do not protect against louse typhus. MOSING (p. 1058) shows that in mice inoculated with the Weigl vaccine the response to the rickettsia-agglutination test, and the protection afforded, vary according to the dose of vaccine given. STEINER (p. 891) thinks that skin reactions to the Weigl vaccine, in persons who have previously received it, are probably due to sensitivity to albumin from the bodies of the lice used.

The epidemic-typhus vaccine of the U.S. Army was very effective in preventing death, but the low incidence of the disease in Europe was due largely to MYL

or DDT powders. SADUSK (p. 811) shows that the ether-treated yolk-sac vaccine of the Breinl strain given in 3 (later 2) doses at intervals of 7–10 days, with refresher doses every 6 months (later at the beginning and middle of the typhus season) protected against epidemic, but not against murine infection. GILLIAM (p. 408) in Egypt showed that one or two doses of Cox vaccine had some effect in reducing the severity of typhus subsequently acquired, but little in prevention; three doses, however, did reduce the attack rate. BERKE (p. 512) used the Cox vaccine with some success in Afghanistan.

GROUPE *et al.* (p. 197) describe the methods they used to increase the yield and potency of typhus vaccines prepared from infected yolk sacs, but for details the original should be consulted. BERKOWITZ (p. 513) has increased the yield of yolk-sac cultures of epidemic and murine rickettsiae by inoculating with a small dose on the 7th day, which allows the embryo to live 11 days longer, when a good growth is obtained.

HAAGEN and CRODEL (p. 196) describe a dried vaccine of yolk-sac cultures of murine and epidemic rickettsiae which, although not suitable for general use, had anti-infectious properties when tested in man (in Germany during the war), in that it apparently was effective against subsequent attempts at virulent infection.

FAJERSTEIN and BESDENJESZNICH (p. 409) found that vaccination with 3 doses gave definite though not complete protection against typhus in Russian railway workers, and that after the course had been repeated in successive years the rate of protection increased.

SADUSK and KUHLENBECK (p. 196) refer to an outbreak of illness after the use of live bile-attenuated typhus vaccine in Japan, and emphasize the risks of such a vaccine. In comment, however, MEGAW remarks on the good results achieved in French North Africa with this kind of vaccine.

FLECK (p. 1057) has obtained from the urine of patients with typhus, a substance which, when injected into guineapigs, protects against the disease and produces positive reactions to the Weil-Felix reaction. He used this substance as a vaccine in man during the German occupation of Poland.

Control.—SOPER *et al.* (p. 892) describe the use of louse powders (MYL and DDT) in the control of outbreaks of typhus in Italy during 1943–45. These outbreaks have been referred to several times in this *Bulletin*, but the present authors give much detail of procedure, which should be sought in the original. GEAR and MURRAY (p. 702) state that outbreaks of louse typhus occur almost every year in the Africans of the Eastern Transvaal, but whereas control was formerly difficult, the use of DDT is now likely to eradicate the disease. A rapid slide test has been found useful in detecting the nature of an outbreak. MUSGRAVE (p. 58) tested the lethal capacity to lice of garments impregnated with DDT in various proportions. Shirts holding 0·2 per cent. of their weight of DDT were effective; the DDT persists at high temperatures and the chief loss of insecticidal power is due to loss of impregnated fibres from the surface of the cloth.

Flea typhus

Epidemiology.—MOOSER (p. 191) has reviewed the research work of 20 years on the relationship between murine and classical typhus.

POLLARD *et al.* (p. 574) gave, by mouth, large doses of a saline suspension of yolk-sac material infected with murine typhus, to 6 healthy volunteers, of whom one became ill with a typical attack. They think that consumption of food contaminated by infected flea faeces, or rat urine, may be the cause of some cases of this disease, but in comment MEGAW suggests that in view of the large dose given in the experiment, the occurrence of this form of infection in nature is probably rare.

CODELEONCINI (p. 302) claims to have isolated a murine strain of rickettsiae for the first time in Ethiopia. By subinoculation in lice and guineapigs the strain showed a tendency to develop characteristics of the epidemic type.

RAYNAL (p. 893) states that it is now well known that human typhus in Shanghai is of murine origin. He performed the Weil-Felix reaction on the sera of rats, for several years, and the percentage positive (1 in 100) fell from 10·3 in 1942 to 2·5 in 1945; there was a comparable fall in the number of positive reactions in human sera. In a fuller version of the same paper (p. 1059) he makes the point he has often stressed, that murine rickettsiae can adapt themselves, under exceptional circumstances, to transmission by human lice. Louse-borne epidemics in Shanghai tend to become arrested in hot weather. LIU (p. 574) found rickettsiae in fleas from rats trapped in a poorhouse in Peiping during an outbreak of typhus; a large proportion of the rats (*R. norvegicus*) showed positive Weil-Felix reaction. He also isolated rickettsiae from the mite *Liponyssus bacoti* found on the rats, but he thinks that fleas are the chief, if not the only, vectors.

WILEY (p. 199) thinks that typhus of murine origin is much more prevalent in the United States than the reported figures indicate. In the north it is found only in business areas of towns, but in the south cases also occur in rural districts. For control DDT, calcium cyanide, sodium fluoroacetate and ANTU are all useful. The incidence rate of flea-borne typhus in part of Alabama was 428 per 100,000 in 1943, and HILL and INGRAHAM (p. 894) show that it was about the same in rural as in urban localities, infection being obviously associated with dusty work in rat-infested places. BECK *et al.* (p. 893) discuss the incidence of typhus of murine type in California since 1916.

RUIZ SANCHEZ *et al.* (p. 304) found positive Weil-Felix tests in 16 per cent. of apparently healthy persons in part of Mexico, where murine typhus is common.

POMALES LEBRON *et al.* (p. 198) found positive complement fixation reactions (with an epidemic-type antigen) in about half the rats examined in Porto Rico, but the Weil-Felix reaction was positive in only a small proportion. Typhus of murine origin is common in the area.

Tests.—Using the Fitzpatrick slide technique [this *Bulletin*, 1945, v. 42, 982], NELSON (p. 705) has found the rickettsia-agglutination test valid for differentiating murine from epidemic typhus and Rocky Mountain fever, a result not always obtained with other techniques. This test was more specific than the Weil-Felix and became positive earlier than the complement-fixation reaction, in the 22 cases of murine typhus tested.

POLLARD *et al.* (p. 303) have devised a test in which the faeces of fleas infected with murine typhus are used for complement fixation with homologous immune sera. This provides a rapid method of detecting the infection in the fleas.

Treatment.—DIAZ-RIVERA *et al.* (p. 199) report decided benefit from *p*-aminobenzoic acid in the treatment of a few cases of murine typhus. Methylene blue, either by subcutaneous injection or by the mouth, was found useful in the treatment of mice infected with *R. mooseri*, and KIKUTH and SCHILLING (p. 199) think that it is worth trial in man.

Vaccination; Control etc.—Oz (p. 59) describes the method of preparation of murine vaccine carried out at the Kudus Institution, Jerusalem.

Fleas and other ectoparasites of rats can be well controlled by using DDT (10 per cent. powder) in their burrows, but complete elimination is not achieved (LUDWIG and NICHOLSON, p. 574). On the other hand, if DDT is thoroughly and carefully applied to the haunts of rats, the number of fleas can be reduced almost to zero; DAVIS (p. 705) reaches this conclusion as a result of work on murine typhus control in Texas. In an account of measures taken in part of Texas to control typhus of murine origin, COX (p. 198) shows that by dusting rat runs with DDT a reduction in rat-flea incidence was caused, and that good

results were obtained against the rats themselves by the use of sodium fluoroacetate. The significance of the complement-fixation test in rats is thought to be doubtful. Instructions for the destruction of rats and their fleas, as a measure of control of murine typhus and plague, are given by ELISHEWITZ (p. 1064), who uses DDT and the rat poisons ANTU and sodium fluoroacetate.

Proteus OXK type: vector mite

Epidemiology: *transmission*.—KALRA (p. 575) quotes figures which indicate that mite, flea and tick typhus are widely distributed in India, and that the mite-borne disease is especially prevalent in Bengal, Assam and Madras. *R. orientalis* has been recovered from *Trombicula deliensis* mites, which are abundant at 7,000 feet in the Kumaon Hills. AUDY (p. 577) noted that the differences observed in various parts of Assam in the risk of infection of troops with scrub typhus were correlated with the presence or absence of *T. deliensis*. These mites could be taken to indicate the movements of rats, and by trapping rats an impression of the presence of mites could be obtained.

BRUNEAU and NGUYEN-DINH-DIEP (p. 655) report an outbreak of scrub typhus in a garrison of a fort in Indo-China. All the 46 cases occurred in the 139 Annamite soldiers, none in the 90 Thais; the freedom of the latter may have been the result of immunity due to previous contact with the infection. A few cases of scrub typhus were reported in American troops in China but it is not known how widespread the disease is. MILLSPAUGH and FULLER (p. 705) have found *Trombicula deliensis* on various mammals and birds in Yunnan and Kweichow provinces and this appears to be the first record of this mite from China.

PHILIP (p. 989) studied scrub typhus in part of Japan where it has been endemic for many years, but where the incidence is falling. Complement-fixation tests with different strains of *R. orientalis* gave very diverse results with the same sera, a point to bear in mind. He (p. 990) has written on the identification of the mites of voles in Japan.

In Dutch New Guinea GRIFFITHS (p. 1060) studied rats and their mites in various locations. There was no evidence that the rats (*R. concolor* group) were infected with scrub typhus in the rain forest; but abandoned village and garden areas, and beach and forest margins were definitely associated with transmission of the disease. *Trombicula deliensis* was the common mite.

PHILIP and WOODWARD (p. 305) report their observations on the Trombiculid mites of the Philippines.

JOHNSON (p. 200) states that there is strong evidence that *Rattus praetor* played a part in the epidemiology of scrub typhus in the Solomon Islands during the war.

Aetiology.—GIROUD (p. 304) has studied the relationship between morphological appearance and pathogenic properties of two strains of scrub typhus rickettsiae.

SMADEL *et al.* (p. 513) have found a toxin lethal to mice in yolk-sac cultures of the Gilliam strain of *R. orientalis*, which can be neutralized by highly diluted homologous antisera. Certain other strains did not produce a toxin.

DIERCKS and TIBBS (p. 894) found that the best results for staining *R. orientalis* are given by MacNeal's tetrachrome stain; they give details for its use.

Pathology.—In a study of the pathology of scrub typhus LEVINE (p. 59) shows that the changes are quite similar to those found in epidemic typhus—haemorrhages, perivascular exudation, consolidation of the lower lobes of the lungs. Oedema of the ankles, or collection of fluid in serous cavities, is common. It seems likely that patients who recover show no residual cardiac damage.

TULLIS *et al.* (p. 895), as a result of examining mice, monkeys and one man infected with the Karp strain of *R. orientalis*, are inclined to think that in

scrub typhus, damage to the endothelium of the vessels is much less severe than in Rocky Mountain fever and epidemic typhus, but MEGAW demurs at this, pointing out that different strains of infecting organisms produce lesions of different severity, and quoting other authors who have not found essential pathological differences between the diseases.

WEIL and HAYMAKER (p. 577) report on the pathology of the nervous system in scrub typhus; the chief changes found in 21 fatal cases were engorgement of the vessels of the leptomeninges and cerebrum, sometimes with marked cellular infiltration. Focal nodules were few.

Tests.—In a series of patients with scrub typhus, from Burma and the Philippines, whose sera were examined at various stages by the complement-fixation reaction, in which three strains of rickettsiae were used, BENGTSON (p. 60) found remarkable variations in response. There is, however, no clear differentiation of serological types. Higher and more persistent titres were obtained with this than with the Weil-Felix test. The same author (p. 61) describes the preparation of an antigen from a strain of scrub typhus rickettsiae from Malaya. The organism was grown in yolk sac culture, and the antigen was specific for scrub typhus, giving negative results with other diseases, including those of the typhus group. She (p. 304) describes how the complement-fixing antigen is separated from suspensions of scrub typhus rickettsiae.

BELL *et al.* (p. 514) have noted antigenic differences in three strains of *R. orientalis*, as measured by cross-neutralizing tests.

Clinical findings: treatment.—SAYEN *et al.* (p. 305) report on 200 cases of scrub typhus in American soldiers in Assam and Burma. It was not possible in the first week of illness to tell if the attack would be mild or severe. There was a primary lesion in 60 per cent., and this, with lymphadenopathy, rash, engorgement of retinal veins or oedema of the retina, and Weil-Felix (*OXK*) of 1 in 100 or more, was a useful diagnostic sign. Some degree of pulmonary involvement was usually present, as was albuminuria. The nervous system was involved in a minority of cases, and haemorrhages were common in severe cases. Convulsions, hyperpyrexia, restlessness, tachycardia and cyanosis were ominous signs; the case mortality rate was 8·5 per cent., though in other series it was lower than this.

RIPLEY (p. 200) notes that in one outbreak of scrub typhus in the Pacific, all patients showed some involvement of the central nervous system, from transient toxic cerebral symptoms to evidence of widespread inflammation, with coma and death. The pathological lesions found were similar to those seen elsewhere in the body, focal lesions with necrosis, thrombosis and perivascular infiltration. Many of the patients showed residual manifestations which seemed to be secondary to the changes in the nervous system, but psychotherapy was of some value.

TEMPLETON (p. 896) describes 56 cases of scrub typhus and 4 of "urban typhus" in troops near Kuala Lumpur. The latter could be differentiated from scrub typhus without eschar only by the results of the Weil-Felix test and by its relative mildness.

MCLIMANS and GRANT (p. 706) show that methylene blue, given with food in a concentration of 0·2 per cent., is strikingly effective in reducing fatality from scrub typhus in Swiss mice, especially when combined with administration of oxygen, even when started as late as 192 hours after inoculation. *Para*-aminobenzoic acid was less effective. PETERSON and FOX (p. 813) report that if methylene blue or toluidine blue is given in food to mice infected with the Karp strain of *R. orientalis*, even as late as a short time after the onset, there is substantial therapeutic effect. The corresponding dosage could not be tolerated by human beings, and intravenous injection in adequate doses causes

haemolytic anaemia. Nevertheless, the results are encouraging, especially when *p*-aminobenzoic acid is given at the same time.

Vaccination.—LEWTHWAITE *et al.* (p. 410) describe the techniques they adopted in cultivating *R. tsutsugamushi* (*R. orientalis*) in the yolk sacs of hens' eggs, for the purpose of preparing vaccines. Details should be sought in the original. Antigens suitable for complement-fixation and rickettsia-agglutination tests could not be obtained in this way. [It will be remembered that vaccine for scrub typhus was eventually obtained from infected lungs of cotton rats.] HENDERSON-BEGG and FULTON (p. 577) standardized the scrub typhus vaccine prepared from lungs of cotton rats by a simple technique for counting the rickettsiae. WALKER (W. T.) (p. 706) shows that scrub-typhus vaccine prepared in England was effective in reducing the severity of attacks of the disease, in 16 cases, even if only one dose had been given. On the other hand, CARD and WALKER (J. M.) (p. 707) could find no satisfactory evidence that the attacks were favourably influenced in 33 men in S.-E. Asia. Not all had received the full course.

Indeterminate type : vector tick

STEINITZ (p. 307) reports, for the first time, a case of boutonneuse fever in Palestine.

BENGTSON (p. 812) discusses nomenclature of the rickettsiae of Rocky Mountain fever and of murine typhus ; readers should consult the original for details.

HUMPHREYS and CAMPBELL (p. 758) have found evidence of infection with Rocky Mountain spotted fever in collections of *Dermacentor andersoni* made in British Columbia and Alberta. They make the point that failure to recover *R. rickettsi* from ticks should not be relied upon as an indication that an area is free from infection ; there may be strains which are mild for guineapigs but virulent for man. BUSTAMENTE and VARELA (p. 656) found *Amblyomma cajennense* naturally infected with Rocky Mountain spotted fever in Veracruz, Mexico.

VALLEJO-FREIRE (p. 708) shows that the rickettsia of tick-borne typhus of Mexico is apparently identical with that of Rocky Mountain spotted fever of North America and of Brazil. He proposes the name spotted fever for this disease, but in comment MEGAW shows that this name, which has been applied to other diseases, is less suitable than tick-typhus.

Discussing the Weil-Felix reaction in Rocky Mountain spotted fever, PLOTZ (p. 201) stated that the usual reaction is of the *Proteus OX19* type, but that the *OX2* titre is sometimes high, and that if it is 1 in 320 or more the disease can be suspected. In comment MEGAW draws somewhat different conclusions from the data given, and thinks that either the *OX19* or the *OX2* titre may vary from 0 to ++++.

DE PAULA (p. 201) describes vesicles on the palate and white ulcers on the fauces, in cases of typhus [presumably tick-borne] in Minas Gerais.

FLINN *et al.* (p. 413) report good results from *p*-aminobenzoic acid in human cases of Rocky Mountain spotted fever. It is rapidly excreted in the urine and repeated administration is therefore necessary. The authors gave 4–6 tablets (each of 0·5 gm.) every 2 hours, to a total dosage of 50·4–327 gm. RAVENEL (p. 708) writes very favourably on the effect of *p*-aminobenzoic acid in Rocky Mountain spotted fever, as a result of its use in 5 cases. ANIGSTEIN and WHITNEY (p. 412) think that administration of calcium gluconate together with *p*-aminobenzoic acid increases the value of the latter in experimental Rocky Mountain spotted fever in guineapigs.

Complement-fixation reactions were carried out on the sera of 40 patients (in India) whose Weil-Felix reactions were of the *OX19* or *OX2* type, by

SEATON and STOKER (p. 576), who used murine and Rocky Mountain spotted fever antigens. Of 18 positive for murine typhus the Weil-Felix was of *OX19* type in 14 ; of 16 positive for Rocky Mountain fever 12 gave the *OX2* type of reaction. Controls were negative. The authors therefore regard this as further evidence of the presence of tick typhus in India. KALRA (p. 575) has isolated strains of rickettsiae (one from a patient in Poona and one from *Haemaphysalis leachi* var. *indica* in Imphal) which show some antigenic relationship to *R. rickettsi*.

PREOBRASHENSKI (p. 898) describes the tick typhus of the Soviet Far East, which is probably transmitted by *Dermacentor sylvarum* and *Haemaphysalis concinna*. PETRJAEV (p. 515) in Soviet Asia describes a disease which he claims is tick-borne, and in which, after a febrile period of 8–10 days, the Weil-Felix reaction with *Proteus OX19* becomes strongly positive.

A small outbreak of tick typhus was reported by ANDREW *et al.* (p. 202) from Queensland, Australia. There was an eschar with associated lymphadenitis in most of the cases, and in two an adult tick was found at the site of the lesion. It seems likely that *Ixodes holocyclus* is the tick concerned, but others occur in the area. The Weil-Felix reaction gave results somewhat like those reported in Rocky Mountain fever, but complement-fixation tests on the sera of the patients failed to show any immunological relationship with that fever or with S. African tick-bite fever, boutonneuse fever, epidemic or murine typhus. The rickettsiae were cultivated by PLOTZ *et al.* (p. 204), and the sera of animals infected with them reacted to the homologous antigen, but not to the antigens of other fevers of the typhus group, including Q fever, though there was some rather indefinite evidence of immunity to S. African tick-bite fever and murine typhus, which may have been non-specific. The rickettsia is probably a hitherto undescribed species. FUNDER and JACKSON (p. 204) report their laboratory comparison of these tick-typhus rickettsiae with murine strains ; there was some incomplete cross immunity. FENNER (p. 514) found low-titre positive complement-fixation reactions with the sera of 8 opossums, bandicoots etc. tested with an antigen from a rickettsia of North Queensland tick typhus. The animals were from an area in which the disease had been reported.

Q fever

In 1945 a disease which occurred in British and American troops in Italy, and which had previously been found in Greece, was shown to be Q fever. The diagnoses made before this identification were atypical pneumonia and Balkan grippe. Q fever had not hitherto been seen outside Australia and the United States. A series of papers in the *American Journal of Hygiene* describes the steps of the investigation made :—

ROBINS and RAGAN (p. 62) show that the onset was sudden, with fever and cough. Signs of patchy consolidation of the lungs appeared, verified by X-ray ; there were no deaths. Blood cultures were sterile, the Weil-Felix test negative, but *Rickettsia burneti* was isolated 16 times in 20 attempts, by inoculation of guineapigs. Sulphonamides and penicillin were useless.

In five of the outbreaks the possible modes of infection were studied, and ROBBINS, GAULD and WARNER (p. 63) noted that the men affected in one unit were those who had slept in, or entered, the loft of a barn in which pigeons, rats, larval ticks, fleas and mites were found. They think that as few of the men complained of bites, an insect vector was unlikely, but inhalation of dust containing dried excreta of animals may have been a factor. There was no evidence of person-to-person transmission.

The rickettsiae were isolated from 16 patients through guineapigs ; they grew readily in yolk sacs of chick embryos. ROBBINS, RUSTIGIAN, SNYDER and SMADEL (p. 64) show that different strains, from Italy and America, gave

different results with the complement-fixation test on sera from human cases and from guineapigs; these differences are probably quantitative, and they were not apparent in the rickettsia-agglutination test.

Robbins and Rustigian (p. 65) think that in the laboratory outbreak which occurred in Italy, the infection was probably acquired by inhalation of air infected usually in the process of yolk-sac culture work.

Feinstein *et al.* (p. 66) describe the symptoms and signs of 143 men whose attack of Q fever began in the United States after a voyage of 9 days from Naples. In most of them there were middle- and lower-zone pulmonary lesions visible on X-ray, which differed in distribution and character from those of primary atypical pneumonia. Similar signs were seen in some men who had no symptoms. Diagnosis was confirmed serologically.

The U.S. Commission on Acute Respiratory Diseases (p. 67) could find no explanation of this outbreak, which involved other units which had been at the same camp in Italy. They think that an arthropod vector may have been involved, while the men were cleaning the camp before leaving it, and were sleeping in the open. The causal organism was not isolated, but complement-fixation tests were usually positive in rising titre. Some positive results were found in another unit which had apparently escaped infection. The Commission (p. 68) gives details of the identification and characteristics of a strain of Balkan grippe rickettsiae isolated in guineapigs in Greece. Sera of guineapigs inoculated with this strain, and of human patients, gave positive complement-fixation tests with antigens from Australian or Italian *R. burneti*; and rickettsia-agglutination tests on sera of guineapigs or patients gave similar results with this and the Australian and Italian antigens.

The Commission (p. 69) recounts the history of the laboratory infection referred to above; rickettsiae were isolated from the blood of some patients and the pleural fluid of one. Symptoms were severe, but the infecting dose (presumably inhaled during manipulation of infected yolk sac material) may have been heavy.

Cheney and Geib (p. 70), having seen cases of atypical pneumonia in Panama, inoculated guineapigs with the blood of some of the patients, and found that one of them was a case of Q fever, of which the rickettsiae showed cross immunity with the standard American strain. The patient had been in the area for 3 months; no indication of the mode of transmission was found.

Topping *et al.* (p. 70) show that 6 strains of Q fever rickettsiae from widely different sources grew readily in yolk sac cultures and were similar in morphology. Five of them showed complete cross immunity (the sixth could not be tested) but the various antigens were not equally sensitive in the complement-fixation test.

Blanc *et al.* (p. 709) isolated three strains of *R. burneti* from *Hyalomma savignyi* (? *H. aegyptium*) in southern Morocco. Blanc *et al.* (p. 898) give reasons for their view that the gerbil *Meriones shawi* is a host of Q fever in Morocco, where *Hyalomma savignyi* is the vector.

Huebner (p. 709) describes an outbreak of Q fever at the National Institute of Health, Bethesda, U.S.A., where 6 strains were being investigated. The outbreak was closely associated with preparation of yolk-sac antigen, involving high-speed centrifugation and treatment with 0·5 per cent. formalin, which has not been found lethal to this rickettsia. In comment, Megaw remarks that it is difficult to reconcile the findings with any other hypothesis than the inhalation of droplets of infected yolk-sac material. Persons who had suffered from the disease during an outbreak in 1940 were not this time affected, and persons who had received Rocky Mountain fever vaccine were apparently protected to some extent, but not completely; typhus vaccination did not confer any protection. The incubation period was 13–18 days.

Topping and his colleagues (p. 710) describe an outbreak of Q fever in stock handlers and slaughterhouse workers in Texas who were probably infected by dust derived from material contaminated by the excreta of a group of apparently healthy cattle. There was no evidence of transmission by ticks. X-ray usually revealed lesions similar to those of atypical pneumonia. In complement-fixation tests with Q fever antigens, rising titres were found to 1 in 320 in 4–5 weeks. *R. burneti* was isolated from two patients through mice, and yolk-sac cultures were readily obtained.

Rickettsialpox and other diseases

The newly recognized rickettsialpox is described by Huebner *et al.* (p. 411) from New York, where an outbreak of 80 cases took place. The clinical features resemble those of chickenpox, but rickettsiae were isolated through mice from one of 15 patients. There is apparently some degree of cross immunity between this disease and Rocky Mountain spotted fever.

Greenberg *et al.* (p. 707) describe rickettsialpox. Almost all patients showed a primary lesion, a papule which became a vesicle and then a scar. The onset of fever was sudden, and the fever was remittent, ending by lysis in 1–10 days. A rash was present in all cases, lasting 4–7 days, and becoming vesicular. Positive complement-fixation tests were given with an antigen prepared from rickettsiae from one patient, but this antigen did not react with sera from patients with certain other rickettsial diseases, though it did with sera from Rocky Mountain spotted fever.

Greenberg *et al.* (p. 990) give details of the epidemiology of rickettsialpox. Mites (*Allodermanyssus sanguineus*) were found on the walls of incinerators and on mice, and the authors point out that if incinerators are irregularly used they conduce to mouse infestation. Huebner, Jellison and Pomerantz (p. 411) isolated two strains of the rickettsia of this disease (*R. akari*) from mites (*Allodermanyssus sanguineus*) collected from mice and from the walls of incinerators in the areas concerned. Other strains were also isolated from pools of mites, but could not be cultivated in fertile eggs. One of the authors was attacked by the disease three weeks after collecting the mites. Huebner *et al.* (p. 897) have recovered *R. akari* from naturally infected mice at the site of the outbreak of rickettsialpox, and have identified them by various tests. The mice appear to be the natural reservoirs of the disease.

In an interesting paper, Baker (p. 896) describes a hitherto unrecorded species of rickettsia which gives an inapparent infection in voles on an island in the St. Lawrence River, Canada. This is immunologically closely akin to the Karp strain of *R. orientalis*, and is probably transmitted by mites (*Trombicula microti*) found on the voles, and from which rickettsiae were recovered.

A laboratory outbreak of trench fever, in persons employed in feeding large numbers of lice for the preparation of Weigl vaccine, is described by Codeleoncini (p. 307) from Addis Ababa. Lice thought to be " clean " were found to be harbouring rickettsiae, which were apparently identical with *R. quintana*. The symptoms were typical of trench fever. Bühler (p. 1061), and Schäfer and Reuter (p. 1061) give their reasons for thinking that one form of field nephritis seen during the war, may have been due to *Rickettsia quintana*.

Neujean (p. 56) claims to have cultivated rickettsiae in the absence of living cells. With Doucet (p. 57) he describes a rickettsial disease of the Congo, claiming that the finding of rickettsiae in the urinary sediment is one of the best methods of diagnosis. He (p. 57) shows that the mouse-protection test for yellow fever remains valid for patients with Congo typhus. He has noticed (p. 58) that healthy laboratory guineapigs harbour rickettsiae

indistinguishable from those which he has cultivated from the blood of typhus patients, but this latent rickettsial infection does not interfere with the use of the animals for typhus work.

Barlovatz (p. 810) describes an attack of a typhus-like fever, with Weil-Felix reaction (*Proteus OX19*) positive to 1 in 640, which he himself had some 3 months after leaving the Belgian Congo. He suspects that it was the Congo form of typhus with prolonged incubation period. *Charles Wilcocks*

RABIES

Veeraraghavan, N. **Further Observations on the Cultivation of Rabies Virus *in vitro*.** *Indian J. Med. Res.* 1947, Oct., v. 35, No. 4, 237–53. [12 refs.]

The author has previously claimed [see this *Bulletin*, 1947, v. 44, 635] that the aetiological agent of rabies can be cultivated *in vitro* in a medium consisting of sheep brain extract with various additions, and that for this reason it may not be a true virus. In a continuation of this work it is stated that the addition of tryptophane, thiamin, pyridoxine and pantothenate increased the amount of virus obtained in cultures. The maximum titres observed were 5×10^9 LD_{50} per cc., which were obtained 24 hours after adding virus to the culture medium at a concentration of 5×10^5 LD_{50} per cc. Propagation of virus in culture was observed through 4 passages.

[This latter fact, together with the high titres reported in this paper, certainly supports the author's claim that true multiplication is occurring, as opposed to an apparent rise of titre caused by dispersion of virus aggregates or the breakdown of combinations with inhibitory substances. Independent confirmation will be awaited with interest.] *D. J. Bauer*

MALARIA

J. National Malaria Soc. 1948, June, v. 7, No. 2, 148–56. **Medical Research in Malaria : 1947. Report of the Committee on Medical Research** [Haas, V. H., Chairman].

Noyan, A. **Summary of the Free Lecture on Malaria.** *Acta Med. Turcica.* Ankara. 1948, v. 1, No. 1, 32–7, 2 folding maps.

This summary of a lecture which was given at the Ankara Numune Hastanesi in May 1946 is semi-popular, but gives some useful information on the distribution and control of malaria in Turkey.

The malarial regions of the country are shown in a shaded map, prepared by the author for the first Turkish Medical Congress in 1925. This indicates the " first malarial region " which includes districts having average parasite and spleen indices of 25 per cent. or more, and comprises the coastal regions, great river beds and the south-eastern part of the country. The " second malarial region " includes the mountains and high plateaux where the disease is usually introduced from the first malarial region, but where it is not ordinarily prevalent. An anti-malaria campaign has been in action since 1924, and although it was somewhat relaxed during the war, it has been intensified in the last two years with good results : in the army, for example, where statistics are readily available, cases of malaria have fallen by half.

The common anophelines are *A. maculipennis*, *A. sacharovi*, *A. superpictus*. In South Turkey and near Palestine, *A. claviger* and *A. sergenti* are encountered.

Epidemiological conditions are favourable to malaria along the Black Sea and Mediterranean coasts, the river beds, in South-East Turkey and in those parts of Anatolia below 1,000 metres.

In the warmer *vilayets* along the Mediterranean coast, malaria may begin in April–May and last until October–November. Benign tertian malaria is relatively common, but in some districts the subtertian form is more frequent : quartan malaria is less common. Cases reported to the first Medical Congress from various hospitals amounted to 9,971 and comprised 5,436 benign tertian, 4,140 subtertian and only 395 quartan infections.

Malignant forms of the disease are not met with as commonly as they are in the tropics and they are not usually fatal. In the first world war, the Turkish Army recorded 400,000 cases of malaria with a mortality of 4·8 per cent. In 1944–45, the death rate was as low as 0·24 to 0·35 per cent.

Control presents difficult problems ; the malarious districts are the richest and most fertile and attract thousands of workers yearly from the less fertile Anatolia ; the crop time coincides with the malaria season and the workers sleep out of doors, often on flat roofs or in gardens. Some of the houses have thatched roofs which harbour mosquitoes and pools are maintained in some villages to provide water for buffaloes and ducks.

Drug prophylaxis with various formulations of quinine and of atebrin [mepacrine] has been employed and the various methods compared, but comparable results were not available at the time when the paper was published.

H. J. O'D. Burke-Gaffney

SAUTET, J., RANQUE, J., VUILLET, F. & VUILLET, J. Quelques notes parasitologiques sur le paludisme et l'anophelisme en Mauritanie. [**Some Parasitological Notes on Malaria and Anophelines in Mauritania.**] *Méd. Trop.* Marseilles. 1948, Jan.–Feb., v. 8, No. 1, 32–9, 1 map.

In a rapid and incomplete survey of parts of Mauritania, French W. Africa, the following anophelines were found : *Anopheles gambiae*, *A. funestus*, *A. pharoensis*, and *A. rufipes*. The dates of capture in some half-dozen localities are given. Adults were taken in houses and other buildings and larvae in both temporary and permanent waters. Of 307 blood slides examined, 180 were positive as follows : *Plasmodium falciparum*, 133 (52 from children under 15 years of age) ; *P. malariae*, 33 (8 children under 15) ; *P. vivax*, 14 (5 children under 15). Of gametocyte carriers, 4 had *P. malariae* and 22 *P. falciparum* and *P. vivax*. The authors draw attention to the predominance of *P. falciparum* infections, the rarity of *P. malariae* and the still greater rarity of *P. vivax* ; but they admit that owing to the small numbers examined they are unable to draw any conclusions.

H. S. Leeson

MCDANIEL, G. E. & HEMPHILL, F. M. *Plasmodium malariae* **in School Surveys in South Carolina.** *J. National Malaria Soc.* 1948, Mar., v. 7, No. 1, 65–75, 2 maps. [11 refs.]

Between 1937 and 1943 the South Carolina State Board of Health carried out thick-film blood smear surveys among school children in 23 countries. Altogether 106,559 smears were collected from 560 schools for white children and from 916 schools for coloured children. Of this total, 10,902 were from 13 schools for white children and 72 schools for coloured children in which the 295 positive *P. malariae* blood films were found. The percentage positive

P. malariae films for white children were 0·64 and for coloured children 3·23 : thus *P. malariae* infection is primarily an infection of the coloured race in this State.

One or more schools in 15 counties gave positive *P. malariae* smears ; in only 8 of these counties were white children found infected. The counties with most *P. malariae* infection were Calhoun, Berkeley, Dorchester, Orangeburg, Sumter, Georgetown and Clarendon : infection is concentrated along the course of the upper Santee River. *P. malariae* was found most frequently in smears taken in December. *Norman White*

VUILLET, J. & LEVAVASSEUR, G. Excitation biologique des ultra-sons sur des oeufs d'*Anopheles maculipennis*. [**Biological Stimulation of** *Anopheles maculipennis* **Eggs by Supersonic Rays.**] *Méd. Trop.* Marseilles. 1947, July–Oct., v. 7, No. 4, 343–6, 3 charts.

Eggs of *Anopheles maculipennis* were exposed to supersonic radiation produced by powers ranging from 250 milliamps to 1,200 milliamps. The periods of exposure varied from 15 seconds to 15 minutes. In some experiments the radiations were concentrated by a concave mirror and in others reflected from a convex surface. The rate of development of the larvae hatching from these eggs was studied and compared with that of larvae from normal untreated eggs.

It was found that the rate of development was accelerated in those larvae from eggs which had received radiations at powers above 1,050 milliamps and concentrated by the concave mirror. For instance, larvae from treated eggs reached the third instar in six days, while normal larvae were still in the first instar and only reached the third stage after nineteen days. In a few trials done with a convex mirror, no acceleration of larval development was observed. Other trials indicated that, varying the period of exposure, within the experimental limits, at any one power made little difference ; and in July when the mean temperature of the water was 26°C., larvae from treated eggs were still more advanced than those from normal eggs, just as in May when the average water temperature was only 20°C.

In discussing this phenomenon, the authors discard the effect of heat as a cause, because with an exposure of 15 seconds they say the water had no time to warm up, but the reviewer cannot help feeling that there may be a local transitory thermal stimulus which they have overlooked. It appears that only a few eggs can withstand the radiations and remain floating ; these hatch but the majority burst and sink, thus showing that such treatment is very near the threshold of destruction. *H. S. Leeson*

COUTINHO, J. de O. Contribução para o conhecimento das espécies do subgênero Kerteszia (Diptera-Culicidae). Sua importância na transmissão da malária. [**Observations on the Sub-genus** *Kerteszia* **and its Importance in the Transmission of Malaria.**] [Thesis for Doctor's Degree.] Universidade de São Paulo, Faculdade de Medicina. 1946. 87 pp., 2 maps, 2 text figs. and 12 figs. on 3 pls. [Bibliography.] English summary.

DULANEY, Anna D. with the technical assistance of Jane B. PRIEST, Mary L. ALMEDA & B. PARKER. **The Complement Content of Human Sera with especial reference to Malaria.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 1, 320–26, 6 figs. [18 refs.]

With the use of a modification of the method of Kent, Bukantz & Rein [see *Bulletin of Hygiene*, 1946, v. 21, 775] the amount of complement in the blood

of (1) 30 normal individuals, (2) 25 persons with liver disease, (3) 32 persons with non-infectious diseases, and (4) 24 neurosyphilitics before and after induced malaria [presumably *P. vivax*, though this is not stated] was determined.

The authors reach the following conclusions :—

" 1. The over-all complement content of normal human sera (as based on the amount in milliliters required for 50 per cent. hemolysis) is remarkably constant.

" 2. The 50 per cent. hemolytic unit for normal individuals, as determined by the method employed by us, ranged from 0·0032 to 0·006 ml. with a median of 0·0045 ml.

" 3. Day-to-day variations in the complement content of normal individuals appear to be slight.

" 4. The complement level of sera (one sample) from patients with liver disease and from patients with non-infectious diseases of various types did not appear to be depressed. There was no correlation between complement titer and the results of the cephalin-cholesterol test.

" 5. Complement is usually diminished during the course of induced malaria. This decrease may be very slight or in severe disease it may be very marked. In general the complement titer reflects the severity of the disease, the balance between host and parasite. Complement titer cannot be correlated with parasite count, white blood cell count, temperature, number of paroxysms, hours of fever, cephalin flocculation test, or antibody titer.

" 6. In any study of complement as related to a particular disease, it is important that a series of determinations be carried out at short intervals during the course of the disease in order to detect changes which may occur."

A. R. D. Adams

D'Ignazio, C. Malaria e febbre ricorrente. Diagnosi differenziale clinica. [**Clinical Differential Diagnosis of Malaria and Relapsing Fever.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 416–22. English summary (2 lines).

Sarrouy, C., Prost & Cabannes. Un cas d'accès pernicieux palustre chez un nourrisson de trois mois. [**A Malignant Attack of Malaria in an Infant of Three Months.**] *Bull. et Mém. Soc. Méd. Hôpit de Paris.* 1947, Nos. 7/8, 115–17, 1 fig.

Rau, L. **Malarial Diabetes. Report of a Case.** *Lancet.* 1948, July 3, 11–12, 1 fig.

A man of 43 returned from India in June 1947, after six years' residence there. A few weeks later he suffered from frequency of micturition, excessive thirst and loss of weight. He had had malaria at the age of 19. There was no significant family history.

On examination on August 21st, glycosuria was present, but no acetone bodies were found. Ring forms of *Plasmodium falciparum* were found in the blood.

Next day, the patient's fasting blood-sugar was 350 mgm./100 cc. Two days later, he became worse, he felt drowsy and could not walk unaided. The fasting blood-sugar was unchanged but the glycosuria was heavy and acetone bodies were present in the urine. He was given 30 units of insulin thrice daily and a diet of 2,500 calories. Next day, his fasting blood sugar had dropped to 182 mgm./100 cc. For two weeks, the patient improved, the glycosuria disappeared, but the fasting blood-sugar was still raised. On September 12th,

when insulin had been reduced to 30 units twice daily, leading to the reappearance of glycosuria, Paludrine was given in a dosage of 0·1 gm. twice daily for 10 days. The urine then became sugar-free, although the diet was unchanged and the insulin dosage was 30 units a day. By October 9th, the fasting blood-sugar was 104 mgm./100 cc. and by the 31st, the patient was no longer on a restricted diet nor was he receiving insulin.

Three months later, after consistently negative weekly examination of the urine for sugar, the result of a sugar tolerance test was within normal limits.

The author considers that the diabetes was caused by malaria affecting the islets of Langerhans. He refers to two cases of severe subtertian malaria, with sudden death, sections from which were shown to him by Professor R. J. V. Pulvertaft; in these, the capillaries of the islets of Langerhans were completely blocked by red blood corpuscles loaded with parasites (one of these sections is illustrated in the text).

It is presumed that a similar pathological process occurred in the present case, in which the diabetes could be controlled by diet and insulin, and was cured by Paludrine. *H. J. O'D. Burke-Gaffney*

Eyles, D. E. & Young, M. D. **Studies on Imported Malarias. 7. The Parasitological Pattern of Relapsing *Plasmodium vivax* in Military Patients.** *J. National Malaria Soc.* 1948, Mar., v. 7, No. 1, 23–37, 3 figs.

In their studies of relapsing *P. vivax* malaria acquired overseas, the authors examined the blood of their patients twice a week after the treatment of clinical attacks. In 77·2 per cent. of relapse attacks in 351 patients under observation, parasites were found in the blood before fever occurred; this percentage would have been higher had daily blood examinations been practicable. On the average, the first parasites were found 3·5 days before the febrile paroxysm. The median fever threshold parasite count for over 800 relapse attacks was 3,200 per cmm. (mean 6,300). For Pacific cases these figures were 2,952 and 6,030; for Mediterranean cases, 3,836 and 7,250. No significant variation in parasite level was found between early, middle and late relapses.

Pacific cases showed male gametocytes to be present in 29·4 per cent. of 659 attacks, against 55·7 per cent. in the case of 185 Mediterranean attacks, a highly significant difference. Patients with or without gametocytes during one relapse were likely to be with or without, respectively, during the subsequent attack.

Delayed primary attacks, nearly all from the Pacific, occurred on the average 49·1 days after suppressive atebrin had been discontinued; extreme intervals were 7 and 167 days. The median value of the first parasite count after onset of fever in delayed primary attacks was 870 per cmm. for 197 cases. In 63 of these cases in which the onset of symptoms was reported promptly, the median value was 450 parasites per cmm.

The mean interval, without regard to the drug used, from the onset of one to the onset of the subsequent clinical attack was 61·1 days; most relapses had taken place by 120 days. Most patients had no demonstrable parasite activity between relapses, but about 12 per cent. had transient low-level asymptomatic parasitaemia 56 days (average) after the onset of the previous clinical attack and lasting 12 days (average), varying from one to 62 days.

Three hundred and fourteen patients were kept under observation for four months or longer after their last clinical attack. About 25 per cent. of these showed terminal asymptomatic parasitaemia; about half of these persisted for more than a month. These parasitaemias were both remittent and intermittent. They were first observed about 80 days (average) after the last

observed clinical attack. Levels attained by these parasitaemias were usually only one-fourth to one-half the levels noted in the same patients at the time of the previous clinical attack.

Malaria parasites were present in the peripheral blood of Pacific malaria patients 13 per cent. of the time and in Mediterranean patients about 10 per cent. of the time. In both groups, 75 to 80 per cent. of the time of parasitaemia was asymptomatic. *Norman White*

SPITLER, D. K. **Malaria Relapse. Report of a Case Thirty-Six Years after Original Infection.** *New England J. of Med.* 1948, June 10, v. 238, No. 24, 839.

The author describes the case of a Sicilian labourer of 69 years who had lived in the vicinity of Cleveland, Ohio, for the previous 36 years. Previously he had been many years at sea and had called at ports as far as the South Pacific. He stated that he had had one attack of malaria in Sicily, but could not recall his age at the time. He denied any recent hypodermic injections.

He was admitted to hospital complaining of fever " at 4-day intêrvals " and on that day and the next many *Plasmodium malariae* parasites were found in his blood. He was treated with quinine and made an uneventful recovery without further febrile illnesses. The author points out that in this case reinfection was highly improbable and that the case appears to have been a genuine relapse. The importance of keeping a diagnosis of malaria in mind in these cases is emphasized. Latency of this nature indicates the inadvisability of using as blood donors persons who have ever had malaria in the past.

It is suggested that the determining cause of the relapse in the present case may have been trauma, as the patient had fallen on the curb a few days before the onset of his chills, and struck the left side of the trunk, *i.e.* over the area of the spleen, where he had a painful lump on admission.

H. J. O'D. Burke-Gaffney

MAIER, J., BANG, F. B. & HAIRSTON, N. G. **A Comparison of the Effectiveness of Quinacrine and Quinine against *Falciparum* Malaria.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 401–6.

This work was carried out during the war in the 2/7 Australian General Hospital. Ninety-nine patients with *P. falciparum* malaria were treated with quinacrine [mepacrine] and 104 with quinine. The course of treatment lasted 6 days in both groups. The daily doses were divided into 3 parts and were :—

Quinacrine 1·2, 0·8, 0·4, 0·4, 0·4, 0·4 grammes.
Quinine hydrochloride 40, 40, 40, 30, 30, 30 grains.

Patients in both series responded rapidly to treatment. There was no appreciable difference between the two series as regards the rate of disappearance of fever or the rate of disappearance of parasites from the peripheral blood. There was no significant difference in gametocyte production in the two series.

Of the 99 patients treated with quinacrine, 6 developed nervous symptoms, 4 transient maniacal states and 2 epileptiform convulsions.

It was found that adequate plasma levels could be obtained when the total quinacrine administered was reduced from 3·6 to 3·2 gm. *Norman White*

PARANJOTHY, J. T. **Notes on some Cases of Atebrin Psychosis.** *Med. J. Malaya.* 1947, Sept., v. 2, No. 1, 49–51.

The author describes four cases of atebrin [mepacrine] psychosis in Malaya. The first was that of an Indian Mohammedan who suffered from malaria in 1944.

He managed to obtain 20 tablets of Bayer's atebrin : after taking 3 tablets daily for 5 days, his attitude changed from that of a prudent business man to an extravagant and reckless generosity with money and goods, which he distributed purposelessly. When the drug was stopped he recovered inside a week.

The second case was a normally cheerful young Chinese girl who became suddenly solemn after taking some 30 tablets of mepacrine (Lilly) in doses of 3 tablets daily when " she got the fever." She began " discoursing on philosophy " and her relatives believed that she was bewitched. The condition cleared up a few days after withdrawal of the drug.

The third case was that of a Tamil shop assistant of 14, who took quinacrine (May and Baker) for malaria twice daily. After 8 tablets had been taken, his normal meek obedience changed to an aimless and incoherent irresponsibility. He became normal within 3 days when the quinacrine was discontinued.

Finally, the author himself took 18 tablets of quinacrine (one tablet thrice daily) for a malarial relapse. On the sixth evening he developed an anxious and " hunted " feeling, with groundless sensations of impending dangers (*e.g.* an immediate flooding of the river, an earthquake, homicidal attacks upon himself). He was vaguely aware of the unreality of these fears and he went home to bed and was normal next morning.

The author adds that none of four Army Medical Officers from whom he made enquiries had had a single case of mepacrine psychosis, although they had used the drug widely in prophylaxis and treatment [see also this *Bulletin*, 1947, v. 44, 763 ; 1948, v. 45, 237, 398]. *H. J. O'D. Burke-Gaffney*

FIELD, J. W. **Paludrine : a General Review.** *Medical No. 3 of 1947, Malaria Advisory Board, Malayan Union.* Kuala Lumpur. 1947, pp. v+42, 21 figs. [43 refs.]

It is pleasant to see that Dr. Field, after the recent enforced circumscription of his activities, has renewed his interest in malariology. For the benefit of others deprived of access to the recent medical literature in Malaya, he has reviewed the development and the present position of paludrine as an antimalarial. After a competent survey of modern theories on the cycle of the malaria parasites, and the current views on the existence of the exo-erythrocytic schizogonic cycle [the factual existence of which has since been demonstrated in monkeys and man—this *Bulletin*, 1948, v. 45, 388, 482] there follows an account of the action of paludrine on the sporozoites and the pre-erythrocytic forms, and on the exoerythrocytic cycles in avian and [presumably] in the human infections. The chemistry, pharmacology, and toxicity of paludrine are reviewed, as are the methods of chemical estimation of, and tests for, the drug. The data available on the prophylactic and suppressive actions of paludrine, and its therapeutic dosage and employment, are eclectically considered. [This excellent review admirably fulfils the purpose for which it was written, and will doubtless be in demand elsewhere.] *A. R. D. Adams*

BETTINI, S. Su alcuni casi di malaria trattati con il Paludrine. [**Cases of Malaria treated with Paludrine.**] *Riv. di Parassit.* Rome. 1948, June, v. 9, No. 2, 107–11. English summary (2 lines).

The author reports the treatment of 112 patients suffering from malaria, in Sardinia, with paludrine—94 *P. falciparum*, 14 *P. vivax*, 1 *P. malariae* and 3 mixed infections. The adult dosage was 100 mgm. three times a day for 10 days and thereafter once a week during the three months' stay of the author at Posada. In 77 of the *P. falciparum* cases, fever disappeared within the first

two days of treatment and did not reappear during the period of observation : in the remaining 17 cases typical febrile attacks occurred at some time after the first five days of treatment. Asexual parasites disappeared from the peripheral blood after the first or second day of treatment. Gametocytes appeared in the blood of 51 of the 94 patients infected with *P. falciparum* after the 5th day of treatment.

P. vivax parasites disappeared from the blood within 2 or 3 days of the beginning of treatment except in one case in which they persisted for 4 days.

In the *P. malariae* patient, parasites persisted in the blood for 6 days.

Norman White

i. Srivastava, R. S. **Final Report on the Field Trials of " Paludrine " in Selected Hyperendemic Malarious Areas of Naini Tal Tarai in the United Provinces (11th September to 31st December, 1946).** *Indian J. Malariology.* 1947, Sept., v. 1, No. 3, 361–3.

ii. Jafar, M. **Preliminary Report on the Use of Paludrine in the Field.** *Ibid.* 365–8.

iii. Ghosh, B. N. **Preliminary Report on the Result of Treatment of Malaria with Paludrine.** *Ibid.* 369–71.

iv. De, M. N. & Datta, P. N. **Final Report on the Study of 58 Cases of Malaria treated with Paludrine.** *Ibid.* 373–81.

v. Parekh, J. H. & Boghani, B. P. **Report on the Use of Paludrine Tablets.** *Ibid.* 383–7.

vi. Lomax, P. H. **Paludrine Treatment Enquiry in Assam.** *Ibid.* 389–93.

vii. Afridi, M. K. **A Critical Review of Therapeutic Trials on Paludrine carried out in India during 1946.** *Ibid.* 347–60.

i. This trial was conducted in a village community. The dosage of paludrine employed was a single one of 300 mgm. administered by the medical officer personally ; alternate cases were treated with 300 mgm. of mepacrine daily for 3 days. During the period 11th September to 31st December, 1946, 138 cases were treated, 76 with paludrine and 62 with mepacrine. Of the 76 paludrine-treated cases, 37 were due to *P. falciparum*, and 22 *P. vivax*, while 17 showed no malaria parasites : of the mepacrine-treated cases, 29 were *falciparum*, 20 *vivax*, and 1 *malariae*, 12 were blood-negative.

From this observation the author concludes :—

" (I) Paludrine in the dosage in which it was administered (300 mg. single dose) controlled malarial attacks quicker than mepacrine. The fever touched normal in 24 hours in 42 per cent of paludrine-treated cases against 16 per cent of mepacrine-treated cases.

" (II) In an hyperendemic area like that of the Naini Tal Tarai, it is very difficult to evaluate the relapse-preventing properties of paludrine, because of the difficulty to ascertain whether a person had actually relapsed or had been reinfected. If the cases which had a recurrence of fever in these areas were cases of relapses, paludrine did not show any advantage over mepacrine in its relapse-preventing properties.

" (III) No toxic effects were noticed."

ii. This trial was conducted in a hyperendemic malaria area in a rural setting 35 miles from Calcutta. A single dose of 300 mgm. of paludrine was given to adult patients, a half or a third of this to children under 12 years of age. All doses were given personally by the medical officer. Of the 492 patients treated only 246 had a parasitaemia (119 *falciparum*, 70 *vivax*, 30 *malariae*, 12 *falciparum*+*vivax*, 10 *falciparum*+*malariae*, and 5 *vivax*+*malariae*).

The author concludes as follows :—

"—— A dosage of 300 mg. given as a single dose was successful in resolving the clinical attack in 3 days in 81 to 87 per cent of cases in all types of infection both as regards fever and parasites."

Parasitic relapses occurred after this treatment in all three infections.

iii. This trial was conducted at the Carmichael Medical College, Calcutta, on 20 patients suffering from clinical malaria with parasitaemia (10 *falciparum*, 6 *vivax*, and 4 mixed infections). These had had no antimalarial treatment for at least 6 weeks prior to treatment with paludrine. The dosage employed in 6 cases (4 *falciparum*, and 2 *vivax*) was a single one of 100 mgm., and in the others 100 to 200 mgm. daily for 2 to 5 days.

The author gives the following summary :—

" —— paludrine is a safe drug to use and will stop clinical attacks of malaria in doses which produce no untoward symptoms. In the above series a minimum single dose of 100 mg., and a maximum of 700 mg., in five days were required to make the patient fever free and parasite free. It had little effect on the sexual forms of the parasite ——."

iv. This study was made at the Medical College Hospital, Calcutta, on 58 cases of malaria (20 *falciparum* and 38 *vivax*), with parasitaemia. These were treated in 5 groups with doses of paludrine ranging from 600 mgm. daily for 2 days followed by 300 mgm. daily for 5–6 days [total 3,000 mgm.] down to 200 mgm. daily for 2 days only. All were free of parasites by the 96th hour of treatment, but the pyrexia persisted in some cases beyond this, and was usually evident for a day or two after the blood had become negative.

The author considers the drug " an excellent and effective remedy " and thinks dosage must be continued after the peripheral blood is clear of parasites as the fever persists after this.

v. This work was done in the Sir J. J. Hospital, Bombay, on 50 cases of malaria with parasitaemia (26 *vivax*, 20 *falciparum*, 3 *malariae*, and 1 mixed). The dosage employed ranged from a single dose of 100 mgm. to 600 mgm. daily for 10 days [total 6,000 mgm.]. The variation in dosages had little influence on the immediate result, all attacks ending in a few days. Subsequent dosage once weekly, it is suggested, " could indefinitely prevent malarial infection from recurring."

vi. This study was undertaken in two isolated areas under the control of the Assam Railway and Trading Co., Ltd. The experiment was to determine (1) a satisfactory suppressive dosage of paludrine in those not suffering from acute malaria, and (2) the dosage necessary to control an acute attack of the disease. In the first trial, a dose of 100 mgm. of paludrine once a week was given as a prophylactic to 1,678 persons, 294 others untreated served as controls. This dosage for various reasons was not found adequate, so 100 mgm. of paludrine was then given twice weekly to 1,075, and 200 mgm. once weekly to 800 persons ; 246 remained untreated as controls. Two hundred and thirty-five acute attacks of malaria (152 *falciparum*, 61 *vivax*, 15 *falciparum—vivax*, and 7 *malariae*) were treated with single doses of 100 mgm. or of 300 mgm. of paludrine, or with 200 mgm. daily for two days.

The author reaches the following conclusions :—

" 1. As a suppressive, one tablet (100 mg.) of paludrine once a week would probably be adequate, but when dealing with mass administration to a disinterested population, a certain number are bound to miss the weekly dose for one reason or another. One tablet (100 mg.) twice a week reduces the chances of any one going a full fortnight without the tablet.

" 2. The success of suppressive measures is directly proportional to the efficiency of the administrative controls.

"3. Three tablets (300 mg.) of paludrine will terminate a clinical attack and is as satisfactory from this point of view as two tablets (200 mg.) b.d. for two days."

vii. In the above series of papers are recorded the results of trials of paludrine in the field under varying conditions of life and of malarial endemicity in sundry parts of India and of Assam. These trials were conducted by independent workers at the request of the Malaria Institute of India, Delhi. In this paper Lt. Col. Afridi, Director of the Institute, collates and analyses the data contained in them.

After a consideration of the characteristics of paludrine, based on the reports of the original workers on the drug, the author outlines the aim of the inquiry, which, briefly, was to determine whether paludrine was effective against local strains of the malaria parasites (1) as a cure for clinical malaria, (2) as a radical cure of the infections, and (3) as a causal prophylactic or as a suppressive. The trials were conducted in rural dispensaries, in hospitals, in jails, and in tea estates and collieries; details of these are analysed. On the whole, acute *falciparum* infections responded more rapidly to treatment than did *vivax*; there was some doubt about the response of *malariae*, which the author believes on occasions to be delayed.

He concludes with the following summary :—

"1. Field trials on paludrine for the treatment of malaria were initiated in July 1946 in different parts of India under the direction of the Malaria Institute of India. The tests were carried out under varying conditions such as rural dispensaries, hospitals, jails, tea estates and collieries. The results obtained up to December 1946 are analysed and reviewed critically.

"2. The value of different dosage regimes was assessed on 1,891 microscopically diagnosed cases of malaria of which 1,283 were *falciparum* (malignant tertian) malaria, 481 were *vivax* (benign tertian) malaria, 68 were *malariae* (quartan) malaria while the remaining 59 cases showed mixed infections.

"3. Paludrine was found to be as effective against the strains of malaria parasites in India as those tested elsewhere.

"4. A single dose of 0·1 gm. and 0·3 gm. of paludrine effected a clinical cure within three days in 84 to 89 per cent. of cases. The drug was equally effective against the three species of malaria parasites although the response was more rapid in malignant tertian than in benign tertian or quartan. In trials where paludrine and mepacrine were tested side by side the curative action of paludrine in the above doses was equal to that of mepacrine in daily dose of 0·3 and 0·4 gm. for 3 and 4 days respectively.

"5. Neither the prolongation of treatment up to 10 days nor an increase in the dosage of paludrine to 0·6 gm. per day caused any appreciable improvement in the percentage of clinical cure. The re-admission rates caused by relapses and/or reinfections were relatively lower in cases treated with high dosages but none of the regimes tested appeared to effect a complete cure. A follow-up treatment of 0·1 gm. once or twice weekly prevented the recurrence of disease in chronic relapsing cases.

"6. It is suggested that in the present state of our knowledge the most desirable course of treatment for malaria in India both in the dispensaries and the hospitals would be a single dose of 0·3 gm. of paludrine. In majority of cases relapses should be treated as and when they arise, but for those who can be relied upon to take the drug regularly, a follow-up treatment of 0·1 gm. once or twice a week should be prescribed for a minimum period of six months.

"7. Paludrine proved to be a safe drug, free from unpleasant effects and non-toxic even in high doses of 0·6 gm. per day. Patients placed on this drug experienced a feeling of well-being within an hour or two of taking it. It was well tolerated by infants and pregnant women.

" 8. In the small number of cases with toxic or pernicious symptoms tested in these trials paludrine was uniformly successful in effecting a rapid cure."

A. R. D. Adams

SCHNEIDER, J. & MÉCHALI, D. Traitement curatif du paludisme. Etude de l'activité comparée de quatre nouveaux dérivés synthétiques. [**Curative Treatment of Malaria : Activity of Four New Synthetic Derivatives Compared.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 274–82. [Refs. in footnotes.]

In the Cocard Hospital at Fez, 135 patients suffering from acute attacks of either *P. falciparum* or *P. vivax* malaria were treated by one or other of four synthetic drugs, nivaquine, nivaquine B (resoquine), paludrine, or metachloridine. In each case the course of treatment lasted five days. (Nivaquine B is said to be identical with chloroquine.) The results were as follows :

Paludrine (48 patients) : *P. vivax* ; duration of fever 2·77, of parasitaemia 3·88 days. *P. falciparum* ; duration of fever 1·7, of parasitaemia 2·4 days.

Nivaquine B (28 patients) : *P. vivax* ; duration of fever 1·62, of parasitaemia 2·2 days. *P. falciparum* ; duration of fever 1·7, of parasitaemia 2·76 days.

Nivaquine (33 patients) : *P. vivax* ; duration of fever 1·7, of parasitaemia 2·9 days. *P. falciparum* ; duration of fever 1·57, of parasitaemia 2·5 days.

Metachloridine (26 patients) : *P. vivax* ; duration of fever more than 3·4, of parasitaemia more than 4·4 days. *P. falciparum* ; duration of fever more than 2·8, of parasitaemia more than 3·6 days.

None of the four preparations appears to have any effect on *P. falciparum* gametocytes.

The two forms of nivaquine are equally effective against *P. vivax* and *P. falciparum* and are well tolerated : they give results slightly superior to those obtained with the same doses of mepacrine.

Paludrine is as effective as nivaquine against *P. falciparum* but not as effective as nivaquine against *P. vivax*. One case of *P. malariae* infection was treated with paludrine for 10 days before the disappearance of parasites from the blood.

Metachloridine displays inconstant activity and symptoms of intolerance are frequent ; it is not recommended for the treatment of malaria attacks.

Further research is in progress to determine the relative efficacy of the two forms of nivaquine and of paludrine as clinical prophylactics and in the prevention of relapse.

Norman White

PULLMAN, T. N., ALVING, A. S., JONES, R., Jr., WHORTON, C. M., CRAIGE, B., Jr. & EICHELBERGER, Lillian. **A Study of the Prophylactic, Curative and Suppressive Activity of SN-11,437 (Metachloridine) in Standardized Infections of *Vivax* Malaria.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 413–23, 7 figs. [14 refs.]

SN-11,437 (Metachloridine) has been shown to be much more potent than any other drug of the sulphonamide series in avian malaria. It has low toxicity for experimental animals. The studies reported in this paper were carried out at the Illinois State Penitentiary. They included pharmacological studies and observations on toxicity in man, and observations on the antimalarial properties of the drug in volunteers infected with either the Chesson (Pacific) or the McCoy (U.S.A.) strain of *P. vivax*.

Absorption of the drug is rapid. Single doses of 1, 2 or 3 gm. by mouth, given without sodium bicarbonate, produce maximum plasma concentrations in 4 hours. The concurrent administration of sodium bicarbonate sufficient to render the urine alkaline triples the amount of SN-11,437 necessary to maintain a given plasma concentration.

Only four instances of mild toxicity were observed among 73 persons treated with a wide range of doses for periods of one day to three months. A prolonged bleeding time with epistaxis and urethral bleeding occurred in one man who received 27 gm. in 6 days. One volunteer had microscopic haematuria. One subject had nausea and vomiting which subsided during continued treatment. Another had several low leucocyte counts during a three-month period of weekly treatment with small doses.

SN-11,437 is as effective as quinine in terminating a clinical attack of *vivax* malaria but parasites persisted in the blood about twice as long as they did with quinine. Both drugs are equally ineffective in delaying or preventing relapse. Complete suppression of mosquito-induced *vivax* malaria was effected in 9 of 10 subjects receiving 0·25 gm. SN-11,437, or more, once a week. The drug, however, has no prophylactic effect apart from suppression.

Norman White

KUEHL, F. A., Jr., SPENCER, C. F. & FOLKERS, K. **Alkaloids of *Dichroa febrifuga* Lour.** *J. Amer. Chem. Soc.* 1948, June, v. 70, No. 6, 2091–3.
[See this *Bulletin*, 1948, v. 45, 578.]

IRVIN, J. L. & IRVIN, Elinor Moore. **A Fluorometric Method for the Determination of Pamaquine, SN-13276, and SN-3294.** *J. Biol. Chem.* 1948, June, v. 174, No. 2, 589–96, 3 figs.

IRVIN, J. L. & IRVIN, Elinor M. **Apparent Dissociation Exponents of Quinine, Pamaquine, and a Quinolylpiperidyl-carbinol ; Application of an Extended pH Scale.** *J. Biol. Chem.* 1948, June, v. 174, No. 2, 577–87, 5 figs. [24 figs.]

CLIFFE, W. H., CURD, F. H. S., ROSE, F. L. & SCOTT, M. **Synthetic Antimalarials. Part XXIII. 2-Arylguanidino-4-aminoalkylaminopyrimidines. Further Variations.** *J. Chem. Soc.* 1948, May, 574–81.

ASHWORTH, R. DE B., CROWTHER, A. F., CURD, F. H. S. & ROSE, F. L. **Synthetic Antimalarials. Part XXIV. Some 2-Phenylureido- and 2-Phenylthioureido-4-dialkylaminoalkylamino-6-methylpyrimidines.** *J. Chem. Soc.* 1948, May, 581–6.

CROWTHER, A. F., CURD, F. H. S. & ROSE, F. L. **Synthetic Antimalarials. Part XXV. Some 4-Arylguanidino-2- and -6-dialkylaminoalkylaminopyrimidines.** *J. Chem. Soc.* 1948, May, 586–93.

CURD, F. H. S., GRAHAM, W. & ROSE, F. L. **Synthetic Antimalarials. Part XXVI. Pyridyl- and Pyrimidyl-aminopyrimidines.** *J. Chem. Sos.* 1948, May, 594–7.

HAWORTH, R. D. & ROBINSON, S. **Synthetic Antimalarials. Part XXVII. Some Derivatives of Phthalazine, Quinoxaline, and isoQuinoline.** *J. Chem. Soc.* 1948, June, 777–82.

CUTHBERTSON, W. W. & MOFFATT, J. S. **Contributions to the Chemistry of Synthetic Antimalarials. Part VI. Some Derivatives of 1 : 3 : 5-Triazine.** *J. Chem. Soc.* 1948, May, 561–4.

VAN RIEL, J. Essai de prophylaxie causale et de traitement de la tierce tropicale par la paludrine. [**Evaluation of Paludrine as a Causal Prophylactic and in the Treatment of Malignant Tertian Malaria.**] *Ann. Soc. Belge de Méd. Trop.* 1948, Mar. 31, v. 28, No. 1, 85–95.

The Mining M.G.L. in Kivu in the Belgian Congo has some mines situated in low-lying areas which are extremely malarious and others at high altitudes

where there are neither anophelines nor malaria. In April 1947, 21 workers were sent from the malaria-free regions to work for a month at Biaboye where anophelism was very intense and where the population was very heavily infected with malaria, almost exclusively *P. falciparum*. During the previous three months none of these men had shown any clinical or parasitological sign of malaria. Their blood had been examined on three occasions during the month prior to their departure. On arrival at Biaboye ten of the men served as controls ; each of the remaining eleven received a tablet of 100 mgm. of paludrine three times a week.

Nine of the ten controls developed clinical malaria between the 20th and 24th days of their stay at Biaboye ; the tenth had parasitaemia which was treated before the onset of fever. All these infections were with *P. falciparum*.

All the treated but one remained completely free from any sign of malaria during their month's stay at Biaboye. The one exception developed an attack of *P. falcpiarum* malaria on the day of his departure. On their arrival back at their malaria-free camp the ten men who had remained free from any sign of infection received their last tablet of paludrine, some 40 hours after the last possible bite of an infected mosquito. They were kept under observation for five months. Only two of the ten remained free from malaria throughout this period. Two developed malaria 16 days after the termination of prophylactic treatment ; three after 25 days ; one after 32 days ; one after 52 days and one after 76 days. Of the nine patients who developed malaria in spite of prophylactic treatment five had *P. falciparum* infection, two *P. vivax* and two *P. malariae*. This is remarkable for in Biaboye it is exceptional to find any parasite other than *P. falciparum*.

To determine the relative efficacy of paludrine in the treatment of attacks of *P. falciparum* malaria, 112 patients were treated with two tablets of 0·5 gm. hydrochloride of quinine a day ; 127 with three tablets of 0·1 gm. atebrin [mepacrine] a day ; and 156 with three tablets of 0·1 gm. paludrine a day (adult doses). All three drugs appear to have been equally effective. Gametocytes appeared with very much greater frequency in the paludrine-treated group than in the other two. The author was unable to verify the action of paludrine as a causal prophylactic in the field. *Norman White*

MAIER, J. **A Field Trial of Chloroquine (SN 7618) as a Suppressive against Malaria in the Philippines.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 407–12.

An endeavour was made to test the value of chloroquine as a suppressive of malaria among two engineer forestry companies stationed on the eastern coast of the Bataan peninsula in the Philippines. The men who were taking daily doses of mepacrine had the medication changed to one tablet of chloroquine (0·3 gm. free base) per week. Unfortunately for the purpose of the experiment there was practically no malaria transmission during the course of the trial. There was indirect evidence, however, that the weekly dose of chloroquine was as effective as the daily dose of mepacrine. One of the Forestry Companies was heavily " seeded " with malaria, acquired in New Guinea. Scanty malaria parasites had been found in the blood of 12 of the 136 men while they had been taking daily mepacrine, though there was no clincal malaria. After one month of chloroquine treatment all smears were negative and remained so.

Of the 350 men placed on chloroquine treatment three had to be taken off the drug because of relatively severe gastro-intestinal symptoms after each dose. Twelve men had mild headaches each time they took the drug. No ocular symptoms were noted. *Norman White*

Craige, B., Jr., Whorton, C. M., Jones, R., Jr., Pullman, T. N., Alving, A. S., Eichelberger, Lillian & Rothman, S. **A Lichen-Planus-like Eruption occurring during the Course of Chloroquine Administration.** *J. Clin. Investigation.* 1948, May, v. 27, No. 3, Pt. 2, 56–9, 4 figs. [10 refs.]

"Of 30 healthy volunteers who were given chloroquine for one year in a dosage in excess of that required for antimalarial suppression, two developed cutaneous eruptions simulating the rash occasionally caused by quinacrine. The patients had no serious systemic symptoms and the eruptions disappeared promptly when the drug was discontinued.

"Three months after the end of chloroquine administration the drug was readministered to Case 1 at a dose of 0·3 gram a day for 17 days without reappearance of the eruption. Two months after the termination of the chronic toxicity study, Case 2 resumed taking chloroquine in a dose of 0·3 gram twice a week. No cutaneous eruption developed in six months' drug administration."

Schneider, J., Dignat, M., Voron & Sfar, M. Prophylaxie collective du paludisme par la prémaline dans la région de Gabès (mai–novembre 1946). [**Mass Prophylaxis of Malaria with Premaline in the Gabes Area, May to November, 1946.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 194–8.

Malaria had been particularly severe in the Gabes region of Tunisia in 1944 and 1945. The outbreak of *P. falciparum* malaria in the latter year was very serious; very few of the inhabitants either European or indigenous escaped malaria in 1945. The appearance of numerous new breeding places for *Anopheles* and the extension of old breeding grounds were responsible for excessive mosquito prevalence. Pending the execution of large-scale anti-larval work it was decided to give suppressive treatment with premaline to the whole population, numbering 32,880. Treatment was begun on the 1st May 1946; all the confirmed cases on that date, 67 in number, were adequately treated. Everyone received premaline, 3 tablets for adults, once a week during the first month and thereafter every ten days till the end of November. [One tablet of premaline contains quinacrine 0·1 gm., rhodoquine 0·005 gm. and praequine 0·005 gm.; see Dupoux *et al.*, this *Bulletin*, 1938, v. 35, 566.] The results were satisfactory. The spleen index of children fell from 35·27 to 17·27 per cent. and of adults from 10·27 to 6·5 per cent. during the period of drug administration. The fall in the parasite rates was from 14·21 to 0·61 per cent. in children and from 6·87 to 1·25 per cent. in adults. The total number of confirmed cases of malaria during the whole season was but 27; 10 of these were in the Ketana area where numerous nomads who had arrived for the date harvest escaped prophylactic treatment.

There was not the least evidence of intolerance to the drug among the 32,880 treated. Anophelism was at least as intense as it had been during the previous year when malaria was severely epidemic. *Norman White*

Schneider, J., Larabi, M. & Balti, M. Prophylaxie collective du paludisme par la nivaquine. Résultats de l'expérience de Ghardimaou (Tunisie). [**Mass Prophylaxis of Malaria with Nivaquine; Results of Experience in Ghardimaou, Tunisia.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 188–94.

This paper gives the results of mass clinical prophylaxis of malaria with nivaquine, a synthetic product formerly named sontoquine [this *Bulletin*, 1948, v. 45, 148]. The experiment was carried out in the region of Ghardimaou, Tunisia, where the population lives in small but stable scattered groups, farms or encampments, and is easy to keep under observation. Drug administration

began on the 1st June 1946 and was continued to 25th November. Anophelines were very numerous after abundant winter and spring rainfall. The number of persons receiving suppressive drugs was 1,347 ; controls numbered 885. Of those given suppressive treatment, 331 received 0·3 gm. quinacrine (mepacrine) once a week ; 312 were given 0·3 gm. nivaquine C (dihydrochloride) once a week ; 166 were given 0·3 gm. nivaquine M (methylene bis-oxynaphthoate) twice a week ; 129 received 0·3 gm. nivaquine M once a week ; 31 received 0·1 gm. nivaquine M daily ; 182 were given 0·3 gm. nivaquine C twice a week ; 196 were given 0·1 gm. nivaquine C daily. All these doses were for adults only.

The results given by the two salts of nivaquine were comparable in every respect, but in view of the superiority of nivaquine C over nivaquine M in the treatment of malaria attacks the latter preparation might well be dispensed with. With a dose of 0·3 gm. once a week, the suppressive results obtained with nivaquine are in every respect as good as those obtained with the same dose of mepacrine. Nivaquine C, 0·1 gm. daily, gave remarkable results ; the parasite index was reduced to zero whereas in an exactly comparable control area the parasite index rose from 4·65 to 10·98 per cent. Among the 84 persons in this control area there were 29 confirmed cases of malaria ; there were none among the 196 taking a daily dose of nivaquine C. In no case was there any symptom of intolerance to nivaquine ; in this respect the drug is certainly superior to mepacrine ; nivaquine does not discolour the skin.

Norman White

McCulloch, R. N. & Waterhouse, D. F. **Laboratory and Field Tests of Mosquito Repellents.** *Commonwealth of Australia. Council for Sci. & Indust. Res. Bull. No. 213.* 28 pp. 1947. Melbourne.

The experiments were made during the recent war to find the best available mosquito repellent material for the fighting services exposed to malaria. Laboratory tests were conducted with the use of a tent containing large numbers of *Aëdes notoscriptus* and *Aëdes alboannulatus*. Other tests were made in cages with *Aëdes aegypti* after a number of culicine species had been investigated for suitability. In the tent 1,000–2,000 adult mosquitoes were maintained, about 100 or so of which might attempt to bite at any time. The mosquito attack was severest at low levels, round the legs and ankles. Tent tests were presumed to be more like natural conditions, but owing to the possible accumulation of vapour, only one or two materials could be tested in the tent per day. This involved the use of large numbers of insects. The cage tests employed much smaller numbers (100 or so) ; only an exposed arm surface was used. In both types of test, the time to first bite was considered very important but the intervals of subsequent bites were also considered in evaluating the repellents.

Field tests were done in New South Wales in coastal bush areas where *Aëdes vigilax* was very common in places (biting untreated limbs at the rate of 25–50 per minute). Other tests were done in New Guinea where *Anopheles punctulatus farauti* and various culicines were the predominant biters.

The tests were made on more than 125 substances and some were tested at several dilutions. The most effective repellents, giving nearly complete protection for 45 to 60 minutes under the most severe conditions, were : Dimethyl phthalate ; 612 (2-ethyl-1,3-hexane-diol) ; "*Stayway*" (diethylene glycol monobutyl ether acetate, etc.) ; oils of *Dacrydium franklinii* (Huon pine) ; *Melaleuca bracteata* ; *Zieria smithii* ; and *Backhousia myrtifolia*. Under similar conditions, Ceylon citronella oil gave protection for no more than twenty minutes.

The vegetable oils were rather unsatisfactory because they were inclined to be irritant to the skin. *Backhousia* and *Zieria* also have a pungent odour. " Stayway " is believed, on the basis of unpublished American work, to have a slight risk of toxicity danger to man. 612 has a distinct smell though in other respects is as good as dimethyl phthalate which was finally considered to be the best all round repellent.

Dimethyl phthalate is colourless, odourless and, apart from slight temporary smarting on application, is harmless to the skin. (Many thousands of men in the army have applied it for many months, often twice nightly, without contracting dermatitis.) " DMP " was definitely better than most other phthalates (ethyl and butyl) tested, though a mixed methyl-ethyl phthalate was nearly as good. The treatment of clothing with dimethyl phthalate prevented mosquitoes biting through it for two or three days.

J. R. Busvine

BERBERIAN, D. A. **The Use of DDT Residual Spray in Malaria Control and its Effect on General Sanitation in Rural Districts.** *J. Palestine Arab Med. Ass.* 1948, Mar., v. 3, No. 3, 49–61, 1 map.

Two experiments were conducted in Lebanon in the Bukâ Plain between the Lebanon and the Anti-Lebanon mountain ranges. The object of the first was to observe the effect of residual DDT spray on the morbidity rates of various infectious fevers in two similar villages, two kilometres apart. All houses in one village were treated in the spring of 1945 and 75 per cent. of the houses in the second village were sprayed in the spring of 1946. The period of study was September and October 1946.

Tabulated results show that in the first village the number of cases of typhoid fever, fevers other than typhoid, diarrhoea, dysentery and conjunctivitis were 230 out of a population of 676 (34 per cent.), and in the second village, 137 out of 687 (20 per cent.). The author's opinion is that there was no factor other than the DDT spraying to account for the lower morbidity rate in the more recently treated village [since the morbidity rates before spraying are not given, there is no evidence to show that any alteration did in fact occur.]

In the second experiment, the object was to test the value of DDT residual spray in the control of malaria. Three highly malarious villages were selected. They are situated overlooking the plain and about a kilometre from the lake and swampy area of Amik. *Anopheles sacharovi* is the chief anopheline, but *A. superpictus* is also found. Preliminary observations were made on the abundance of breeding in the swamp and lake and on the spleen indices of the villagers. Then 5 per cent. DDT in kerosene was sprayed on the surface of the lake and in the houses. In treating the lake, the vegetation was left and no attempt was made to reach the centre. Six sprayings were applied between May and November at intervals of 3 to 5 weeks. Each treatment was followed by a reduction in the numbers of larvae and in the numbers of adults in the houses. The numbers of other insects also diminished to a remarkable extent, but no ill effects on *Gambusia* or other fish were noted.

The author gives the costs of the experiment and describes methods and apparatus; he is satisfied that 5 per cent. DDT in kerosene is an effective larvicide, even without the removal of aquatic vegetation; and that residual spraying of dwellings resulted in the destruction of the insects associated with the dissemination of malaria, dengue, sandfly fever, conjunctivitis, summer diarrhoea of children, dysenteries and enteric, and in a highly malarious area resulted in the reduction of the sizes of spleens of the inhabitants within a period of eight months.

H. S. Leeson

TETZLAFF, F. **Operation of the United States Public Health Service Malaria Control Program.** *Pub. Health Rep.* Wash. 1948, Apr. 30, v. 63, No. 18, 557–63, 2 figs.

Before the war in some States of the U.S.A. no malaria control organization existed, any activity in this direction forming part of the general sanitation programme. The wide extension of control measures during the war years by the Public Health Service of the Central Government to protect military personnel resulted in a more general recognition by the public of the value of these measures. Towards the end of the war, the application of DDT as a residual insecticide to control *A. quadrimaculatus* proved to be so effective that this method became the sole measure of control in many areas with the cessation of the older methods of drainage and use of larvicides.

After the war the situation of the war years was reversed in that it became necessary to protect the civilian population from malaria introduced by returning servicemen. Residual DDT spray operations have been extended to cover all affected areas in the United States. Coincident fly control has been a major factor in the general acceptance and success of the method. It is hoped that the expense entailed will be accepted eventually as a local charge on the rates ; the end result should be a reduction in malaria incidence to the extent that malaria will no longer constitute a significant health problem in the United States. Lastly State and local Health Departments have become familiar with the programme necessary for the control of any insects having a public health significance. *R. Ford Tredre*

CORRADETTI, A. Bases experimentales para la eliminación de la malaria en la Costa del Perú. [**Experimental Basis of Malaria Control on the Coast of Peru.**] Publicaciones de la Dirección General de Salud Publica. Departamento de Malaria. 1947, Aug. 7, 14 pp. 2 graphs.

The author describes the use of domestic spraying with DDT as a measure for the reduction of *Anopheles pseudopunctipennis* and malaria in the coastal plain of Peru.

It is known that in the coastal plain *A. punctipennis* is the principal vector : it is only important when present in considerable numbers. The work was carried out in the valley of Mala, an area in which the Rockefeller Foundation has been studying malaria and applying other measures of control from 1942–46. The area was therefore a very suitable one for the experiment. DDT in kerosene was sprayed on walls of all houses in the valley at the rate of 2 gm. per sq. metre (apparently on a single occasion). The total human population of the area was 8,365. The Rockefeller Foundation had previously established that at the end of the transmission season the parasite rate was between 11 and 28·9 per cent. After the application of the DDT, the figure was always below 1 per cent. at the same time of year. The greater part of the malaria was due to *P. vivax*, but *P. falciparum* and *malariae* also occurred : all three were very greatly reduced by the DDT.

The author states in somewhat general terms that the distribution of the DDT has been followed by a general reduction of mortality due to infectious diseases. He discusses the use of similar methods for the destruction of *Phlebotomus* and the control of verruga peruana. *P. A. Buxton*

J. NATIONAL MALARIA SOC. 1948, June, v. 7, No. 2, 157–65. **Cost Records in Malaria Control. Report of the Committee on Sanitary Engineering** [HENDERSON, J. M., Chairman].

SHORTT, H. E. & GARNHAM, P. C. C. **Demonstration of a Persisting Exo-Erythrocytic Cycle in *Plasmodium cynomolgi* and its Bearing on the Production of Relapses.** *Brit. Med. J.* 1948, June 26, 1225–8, 2 figs.

The demonstration of pre-erythrocytic development of *Plasmodium cynomolgi* and *P. vivax* in liver cells, following inoculation of sporozoites [this *Bulletin*, 1948, v. 45, 388], led the authors to investigate the possibility of the persistence of the developmental forms in the liver after the disappearance of the blood infection. It was hoped in this way to throw light on the mechanism of relapses in malaria. A piece of liver of a monkey was removed by biopsy on June 1st, the blood having shown parasites for the last time on April 24th ; the infection had resulted from the feeding of 680 infected *Anopheles maculipennis* on February 18th. On June 2nd, the blood showed a considerable number of early ring forms of *P. cynomolgi*. The piece of liver was sectioned, and examination of 412 sections revealed two schizonts, one measuring 16μ in diameter and containing about 130 nuclei and the other 30μ in diameter and showing about 500 nuclei. The finding of these schizonts nearly three and a half months after a sporozoite-induced infection is a clear demonstration of the persistence of the exo-erythrocytic cycle after establishment of the blood infection. The occurrence of the two schizonts on the day before the reappearance of the blood infection does not prove that the rings were derived from exo-erythrocytic schizonts but it makes it very probable, in view of the fact that malarial relapses occur long after the blood has been proved to be free of parasites, both by direct observation and by failure to produce infections by blood inoculations. This disappearance of parasites from the blood may be the result of immune bodies developed as a result of the infection or because of anti-malarial drugs. It would seem that the immune bodies are active in suppressing the erythrocytic infection but have no action on the forms which develop in the parenchyma cells of the liver, which are able to continue their development and lead to blood infection when for some reason the active immunity of the host has been impaired. In the observations reported, the reappearance of blood infection on the day following the biopsy may indicate the modification of the immune reaction allowing the merozoites entering the blood stream from the liver to survive. It seems reasonable to suppose that a similar persistence of exo-erythrocytic stages will be found to occur in the case of *P. vivax*, which closely resembles *P. cynomolgi*. *C. M. Wenyon*

WHITMAN, L. **The Effect of Artificial Blood Meals containing the Hydroxy-naphthoquinone M2279 on the Developmental Cycle of *Plasmodium gallinaceum* in *Aedes aegypti*.** *J. Infect. Dis.* 1948, May–June, v. 82, No. 3, 251–5.

Experiments were carried out to test the effect of hydroxynaphthoquinone M2279 on the oöcysts and sporozoites of *P. gallinaceum*. *Aëdes aegypti* mosquitoes were allowed to feed through goldbeater's skin on chicken plasma containing the drug and washed erythrocytes. This solution was held in depressions in a warmed Coors' spot plate and the mosquitoes fed readily provided they had been starved for 48 hours previously ; 25 per cent. of the drug persisted in the mosquitoes for at least 48 hours. The drug was most effective when administered at the same time as the infective feed, completely suppressing oöcyst formation. The number of oöcysts was reduced considerably if the drug was given 48 hours before or 48 hours after feeding, but during their period of growth the oöcysts were completely insusceptible. During the migration of the sporozoites from the gut to the salivary glands, the infection was partially controlled by the drug, but once the sporozoites reached the glands, they became protected from the drug's action. *P. C. C. Garnham*

Simpson, M. L. **Reproduction of the " 3T " Strain of *Plasmodium cathemerium* in White Pekin Ducks.** *Amer. J. Hyg.* 1948, May, v. 47, No. 3, 315–34, 10 figs. [19 refs.]

This is the report of an elaborate and carefully controlled series of experiments on the cycle of *P. cathemerium* in the duck which deserved more interesting results than were actually obtained. The parasite was introduced by blood inoculation into (*a*) young ducks (two weeks old), (*b*) mature ducks and (*c*) canaries, and the ensuing infections were studied and compared. There was the same degree of synchronicity of segmentation in all three groups, *viz.* between 4 p.m. and 10 p.m. in a regular 24-hour cycle, unaffected by artificial conditions of lighting and darkness. In all birds, later in the disease, the synchronicity became less punctual. In canaries, segmentation was even more exactly timed and tended to occur 4 hours earlier in the day. The parasite density was greatest in young ducks and in the group exposed to artificially regulated light. The average number of merozoites per schizont was the same in all the ducks and throughout the 5 days of the patent period of the infection. In canaries, the number of merozoites varied during the course of the disease, probably because the patent period was lengthy and gave time for fluctuations to become manifest.

Late passage infections in ducks gave rise to fewer gametocytes than the earlier ones (a 6-fold decrease), indicating that long residence in the duck inhibited their production. *P. C. C. Garnham*

Bovet, D., Decourt, P., Schneider, J. & Montezin, G. Activité dans le paludisme aviaire de quelques dérivés synthétiques recemment introduits en thérapeutique : nivaquine, nivaquine B, paludrine et metachloridine. [**Activity of Nivaquine, Nivaquine B, Paludrine and Metachloride in Avian Malaria.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 268–74. [16 refs.]

BLACKWATER FEVER

Black, R. H. **The Resorption of Haemoglobin by the Renal Tubules in Haemoglobinuria.** *Ann. Trop. Med. & Parasit.* 1948, Apr., v. 42, No. 1, 90–94, 12 figs. on 2 pls. [20 refs.]

In man and some animals, conditions associated with haemoglobinuria often show eosinophilic granules in the epithelial cells of the convoluted tubules of the kidney. Such granules give the staining reactions characteristic of haemoglobin and are released into the lumen when the cells degenerate. The author suggests that haemoglobin in the glomerular filtrate is absorbed by the tubule cells and its nature modified in some way. *E. T. Renbourn*

TRYPANOSOMIASIS

Geigy, R. Beobachtungen an einer Zucht von *Glossina palpalis*. [**A Note on a Culture of *Glossina palpalis*.**] Reprinted from *Verhandlungen d. Schweiz. Naturforschenden Gesellschaft Zurich.* 1946, pp. 155–8.

The paper describes the maintenance of a culture of *Glossina palpalis* in Switzerland for a considerable period.

The author reviews what is known about the relation of *Glossina palpalis* to temperature. As it is established that at about 13°C. the adult flies are quite torpid and capable of surviving unfed for 10–15 days, he decided to bring them

from the Congo to Switzerland in small gauze cages in an ice box. About 40 per cent. of the flies with which he started arrived alive, 22 males and 98 females reaching Basle. The original number has been increased to some extent by the importation of pupae, but it seems that six generations were reared at the time of writing and that the number of flies was increasing. The insects were kept always at 26°C. and 85 per cent. relative humidity and were offered food daily on guineapigs. Under these conditions one individual fly lived as long as 207 days and one female deposited sixteen larvae. The interval between the emergence from the pupa and the birth of the first larva is twenty-two days and after that births occur almost regularly at ten-day intervals. The duration of the pupal stage is thirty-five days in the female and about two days longer in the male. *P. A. Buxton*

JACKSON, C. H. N. **The Analysis of a Tsetse-Fly Population. III.** *Ann. Eugenics.* 1948, Apr., v. 14, Pt. 2, 91–108, 2 figs.

The author is concerned with the study and analysis of populations of *Glossina morsitans* at Kakoma, Tanganyika Territory. The main body of his material is derived from flies which were marked weekly for a long period and statistical deductions are here given from those results [see this *Bulletin*, 1945, v. 42, 186]. But the author has used a number of other ingenious methods of study and endeavours to check results obtained with one method against those of another. The present paper is stated to be the last of its series: in it Jackson brings together some previous work, modifies certain of his methods and sets down his conclusions. For technical details the reader must refer to the original paper. Here it is only possible to make a brief and general abstract.

The bulk of the paper deals with the author's methods of calculating the actual population of tsetse per square mile, for which a new method is developed based on those individual flies which are marked and then recaptured more than once. He also recapitulates his work on the calculation of death rates and birth rates, a subject on which he has developed a formula, assessing the errors of his estimates. His information on the disposal of individual flies is based not only on the familiar marking method but on unmarked flies introduced into a type of environment not unsuitable to *G. morsitans* though that species does not occur in it [see this *Bulletin*, 1946, v. 43, 312]. The statistical work has revealed short-term fluctuations in death rates and birth rates which cannot be associated with changes in climate, and appears to depend on factors in the fly population. It seems that male *G. morsitans* are relatively inactive during the first two weeks of life and that for that period their death rate may be lower than it is later. This inactivity, which has only recently been discovered, affects the shape of survival curves and the estimate of mean life: the figure, however, still appears to be about four weeks for male flies. The fact that male flies are inactive early in life explains what has already been observed, that if one estimates the age of a sample of wild flies by the wing fray one obtains a figure which is higher than the estimation based on flies which are marked and recovered. The inactivity early in life has caused the author to make a recalculation of his estimate of the whole male population: his previous estimates have to be increased by about 1·4 times. *P. A. Buxton*

HILL, K. R. **The Protein Content of Cerebrospinal Fluid in Trypanosomiasis.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 641–4. [16 refs.]

The most commonly used routine methods of protein estimation for cerebrospinal fluid depend on measurement either of precipitation, as in the Sicard and Cantaloube test, or of opacity, as in various so-called turbidimetric tests. There

is wide variability in the limits of normality given by different workers, even where the same methods are used. This is illustrated by the following figures, culled at random from various authorities :—

Authors	Method	Normal C.S.F. protein in mgm. per 100 cc.
Mestrezat (1912)	Turbidimetric (Diaphanometric)	13–20
Buzzard & Grenfield (1921)	,, (Mestrezat)	–30
Grey (1930)	,, (Proteinometer)	–40
Harrison (1939)	,, (Mestrezat)	10–30
King (1945)	,, (Sulphosalicylic)	20–40
Stitt *et al.* (1945)	,, (Denis & Ayer)	15–40
Panton & Marrack (1945)	,, (Sulphosalicylic)	20–35
Hutchinson & Hunter (1934)	Precipitation (Aufrecht)	20–35
Levinson (1929)	,, (Nissl's)	13–47
Purves Stewart (1924) ...	,, (Aufrecht)	20–30
Saunders (1945)	,, (Sicard & Cantaloube)	–22
French Trypanosomiasis Service Author	,, (Sicard & Cantaloube)	–22
	Turbidimetric (proteinometer)	20–30 (35)

Hill has performed an experiment in which three observers were asked to examine a number of cerebrospinal fluids both by the proteinometer and by the Sicard and Cantaloube methods. The former method consistently gave protein values 1½ to 2 times as great as the latter. Such a discrepancy would be very important where the proteinometer indicates 30 to 40 mgm. per 100 cc., since according to Sicard and Cantaloube (*Bull. et Mém. Soc. Méd. Hôpit. de Paris*, 1916, v. 40, 481) this figure is grossly abnormal, and according to Fairbairn [this *Bulletin*, 1934, v. 31, 559] and Saunders (personal communication) it has a bad prognosis in sleeping sickness, whereas according to Grey (*Arch. Dis. Childhood*, 1930, v. 5, 187) and others, it is within normal limits, or perhaps, at the worst, at the upper limit of normal.

The author considers the Sicard and Cantaloube method to be the method of choice for routine work, since it gives a precipitate which lends itself to accurate measurement more readily than does opacity. Workers who refer to the protein content of cerebrospinal fluid should mention the method used.

[At the International Trypanosomiasis Conference at Brazzaville in February 1948, the recommendations of which are not yet published, it was concluded that the upper limits of the cell-count and total protein content of the cerebrospinal fluid within which a patient should be considered in the lymphatico-blood stage should be 3 cells per cmm. and 0·025 gm. protein per 100 cc., as estimated by the Sicard-Cantaloube method ; that a more precise and, if possible, more rapid method for estimating total protein should be investigated ; and that further investigation should be made into the exact composition of the cerebrospinal fluid in the normal African.] *E. M. Lourie*

Saleun, G. & Chassain, J. Premiers essais de traitement de la trypanosomiase humaine, par la pentamidine en Afrique Équatoriale Française. [**First Trials of Pentamidine against Sleeping Sickness in French Equatorial Africa.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 89–104.

This paper describes in detail the investigation of pentamidine for sleeping sickness, by a number of officers of the Institut Pasteur de Brazzaville and of

the recently established Service Général d'Hygiène Mobile et de Prophylaxie de l'A.E.F. [See also TRINQUIER and ARNOULT, this *Bulletin*, 1948, v. 45, 313]. The findings are, in the main, confirmatory of work already published from other quarters. The first trials in A.E.F. were carried out at the Pasteur Institute, in 1945, when 2 mgm./kgm. [whether dihydrochloride or di-isethionate is not stated] administered intravenously each day for 8–10 days was found to be too toxic. Dosage was then reduced to 1·25 mgm./kgm. for the first injection, 1·75 mgm. the next day, and 2 mgm. daily thereafter for the remainder of the course. Trials were then extended first to the " hypnoseries " in various outlying districts, and finally to the itinerant treatment teams, where a disaster immediately occurred. The first three patients collapsed immediately after their first intravenous injection of 1 mgm./kgm. Two of these individuals recovered within 24 hours, but the third died after 7 minutes of coma and epileptiform convulsions. An error in the dosage actually administered cannot be excluded with certainty. Nevertheless it was decided to use only the intramuscular route of administration for ambulatory treatment in the future.

The toxic effects of treatment are described in great detail. As is well known, the most common and most striking immediate effect is a considerable fall in blood-pressure, occasionally associated with syncope. Transitory albuminuria occurred in only 3·7 per cent. of the cases treated. In only one instance was there the possibility that a significant degree of renal damage might have been due to the treatment. When the intramuscular route was used, toxic reactions were much less frequent, and syncope never occurred, even when the dose was 3 mgm./kgm. It was found that pregnancy does not contra-indicate the use of pentamidine ; [this is of interest in view of the statement, not yet backed by much published evidence, that propamidine tends to produce abortion, see VAN HOOF, this *Bulletin*, 1947, v. 44, 1048].

A treatment-course studied in many of the centres consisted of 8 daily injections, 8 days' rest, and then 8 daily injections again. Where the first three intravenous doses were 1·0, 1·25 and 1·5 mgm./kgm., respectively, it was sometimes 4 or 5 days before trypanosomes were no longer to be found ; but where treatment was by 1·5 mgm./kgm. throughout, it was nearly always the case that trypanosomes could no longer be seen on the day after the first injection. Where treatment began with the lower doses there was transient reappearance of trypanosomes between the 8th and the 11th injections in 4 of 84 cases. Where treatment was by 1·5 mgm./kgm. from the start, this temporary reappearance of trypanosomes occurred in 1 of 61 cases. The authors therefore write that there is apparently a defined period when relapses tend to occur (a " *pointe de rechute* ") during the actual course of treatment, which they say also characterizes the use of certain arsenicals.

In the first trials at the Pasteur Institute, 16 of the 32 cases treated had advanced beyond the lymphatico-blood stage. All the other cases of this report, to the number of 546, were in the lymphatico-blood stage. All were sterilized by the end of their treatment courses and were still well up to the limit of observation, which, in most cases, however, does not seem to have exceeded five months at the time of writing. There was a favourable response in all of 26 cases which had previously proved to be refractory to other remedies, such as suramin, tartar emetic, and various arsenicals. *E. M. Lourie*

SICÉ, A. De quelques réactions au cours d'un traitement par la pentamidine. [**Some Reactions during a course of Pentamidine Treatment.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 159–61.

Mlle. W. R., aged 27, does not seem to take kindly to treatment for sleeping sickness. [She is apparently one of the two accidentally infected ladies about

whom SICÉ has already written, this *Bulletin*, 1948, v. 45, 312.] She was first treated by combined tartar emetic and atoxyl. This had to be stopped after a total of 250 mgm. tartar emetic and 2·5 gm. atoxyl, which caused pain along the veins chosen for injection, headache, and subjective visual disturbances. She then received suramin, first alone at a dosage of 1 gm., then in doses of 0·75 gm. together with neo-stibosan. This gave rise to albuminuria, the appearance of leucocytes and blood casts in the urine, and hyperpyrexia. She was then given pentamidine isethionate in the gluteal regions, 150 mgm. (*i.e.* 3 mgm. per kgm. body weight) daily. There was no particular reaction throughout the 8-day course of treatment, except for mild recrudescence of the renal disturbance. There was then a rest-period of 13 days, after which daily intramuscular injections were started again. At the 4th injection the patient developed a feeling of constriction in the throat, a bitter taste in the mouth, and a painful, tender, red swelling, about 5 cm. in diameter and about 10 cm. from the point of injection. It was freely movable under the skin. In the course of the next few days it assumed various colours and gradually subsided. Daily intramuscular treatment was, however, continued uninterruptedly in the scapular region without further complication, except for fleeting sensations of numbness down the limb on the side injected. The second treatment-course totalled 9 injections. [The tumour was non-fluctuant, but could it not have been a haematoma ?] *E. M. Lourie*

TRINQUIER, E. & PELLISSIER, A. Emploi du 3177 RP par voie buccale dans le traitement de la maladie du sommeil. [**Oral Treatment of Sleeping Sickness by 3177 RP.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 161–5.

This report from the Brazzaville Pasteur Institute deals with the treatment of sleeping sickness by 2224 RP and 3177 RP, prepared by the Société Parisienne d'Expansion Chimique. [The compounds are identical, respectively, with melarsen (FRIEDHEIM, this *Bulletin*, 1941, v. 38, 634) and melarsen oxide (WEINMAN and FRANZ, this *Bulletin*, 1946, v. 43, 207 ; VAN HOOF, this *Bulletin*, 1947, v. 44, 1048)].

Treatment was given orally. The first patient, who was in the nervous stage of infection, developed profuse diarrhoea after 2 doses of 30 mgm. The standard course of 3177 RP adopted for subsequent cases, therefore, consisted of 14 daily doses, comprising 1 of 10 mgm., followed by 4 of 20 mgm., and then 9 of 30 mgm. per adult, irrespective of body weight. This was well tolerated in the lymphatico-blood stage (3 cases) and in the stage of meningeal reaction (5 cases), but not in the meningo-encephalitic stage (2 cases). As a result of the slight evidence obtained on a follow-up period of only 1 month the authors conclude that 3177 RP has a very rapid sterilizing action ; that it can probably cure most cases in the lymphatico-blood stage ; that it has no action in the stage of meningeal reaction ; and that it is dangerous in the meningo-encephalitic stage.

In an addendum, benefit is claimed for 3 early cases treated by 2224 RP, also administered orally. *E. M. Lourie*

TRINQUIER, E. & PELLISSIER, A. Emploi du 2224 RP par voie buccale dans le traitement de la maladie du sommeil. [**Oral Treatment of Sleeping Sickness by 2224 RP.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 260–68.

Compound 2224 RP is identical with FRIEDHEIM's melarsen [see above].

Treatment was given orally in all cases. As a result of earlier findings by FRIEDHEIM and by MURAZ, which the authors describe, and after several unfavourable experiences with other dosages, the course finally adopted consisted of daily treatment for 2 weeks, beginning with 20 mgm./kgm. the

first day, rising by 10 mgm./kgm. daily to 60 mgm./kgm. on the 5th day, and maintained at this level for the remainder of the course, but with a ceiling-dose of 3 gm. This was well supported in all the cases thus treated.

The gland-juice or blood was usually cleared of trypanosomes within 24 hours, but sometimes not until the fourth day. Symptoms rapidly abated in earlier cases, but sometimes became aggravated in the later stages of infection.

Cases treated consisted of 1 in the lymphatico-blood stage, 1 in the stage of meningeal reaction and 18 in the stage of meningo-encephalitis, 10 of which had proved resistant to earlier treatment with other compounds. The records given include results of cerebrospinal fluid examinations at the beginning, at the end, and 1 month after the end, of treatment. The case in the lymphatico-blood stage responded well, and was still well 1 month after a single course of treatment, but this was judged to be inadequate for the other types of case.

E. M. Lourie

SALEUN, G. & CHASSAIN, J. Essai de chimio-prophylaxie de la trypanosomiase humaine en Afrique Equatoriale Française par la pentamidine. [**Chemo-prophylaxis of Sleeping Sickness by Pentamidine in French Equatorial Africa.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 165–8.

The authors report preliminary results of an experiment by CHOUMARA and SOUVEINE in the Oubangi-Chari district of French Equatorial Africa.

On June 18th, 1946, the 409 inhabitants of 3 villages were examined: 144 of these persons were already under observation after previous treatment for sleeping sickness, and 4 new cases were discovered. The remaining 261 persons were given a single intramuscular injection of pentamidine, 4 mgm./kgm. for children of 5–12 years, and 5 mgm./kgm. for those over 12 years of age.

The results of examinations at quarterly intervals, before and after this treatment, were as follows:—

	Time of examination	New cases	Index of new cases *
			Per cent.
Before treatment	1st quarter, 1945	26	5·7
	2nd ,, ,, ...	20	4·8
	3rd ,, ,, ...	4	1·09
	4th ,, ,, ...	10	3·2
	1st ,, 1946	13	4·06
	2nd ,, ,, ...	12	3·8
After treatment	3rd quarter, 1946	2	0·9
	4th ,, ,, ...	0	0
	Jan.-Feb., 1947	0	0

The authors therefore believe that a single injection of pentamidine can protect for 6 to 8 months.

[* The Index of New Cases is calculated as follows, according to the International Trypanosomiasis Conference at Brazzaville, February 1948:—

$$\frac{\text{Total new cases} \times 100}{\text{Total examined, less old cases considered not cured.}}$$

E. M. Lourie

i. Launoy, L. & Jeanpierre, C. Essais sur l'action préventive du diamidino-diphénoxypentane administré *per os* sur la trypanosomose expérimentale à *Trypanosoma equiperdum* du rat. [**Prophylactic Action of Oral Pentamidine against** *T. equiperdum* **Infection in the Rat.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 25–8.

ii. —— & ——. Suite à l'étude de l'action préventive du diamidino-diphénoxypentane administré *per os*, sur la trypanosomose expérimentale à *Trypanosoma equiperdum* du rat. [**Further Studies of the Prophylactic Action of Oral Pentamidine in the Rat.**] *Ibid.* v. 41, Nos. 3/4, 168–72.

i. Thirty-six rats were given a single dose of pentamidine orally, over a dosage-range of 5 to 15 mgm. per 100 gm. body weight. There were 8 deaths from toxic action in the range 7·5–15 mgm., though most of the rats treated with 10 mgm. withstood this amount. Each of the survivors received a single subcutaneous inoculation of 1 million *T. equiperdum* at intervals ranging from 5 to 20 days after treatment. The protective effects appeared in somewhat irregular manner. Complete protection for 7 days may, however, be expected after an oral dose of 5 mgm./100 gm. This is 10 times greater than the dose capable of protecting 50 per cent. of rats for 14 days after subcutaneous administration [Launoy and Lagodsky, *Bull. Soc. Path. Exot.*, 1940, v. 33, 320, and this *Bulletin*, 1947, v. 44, 702].

The therapeutic effect of oral treatment was also investigated. In heavy infections, doses up to 20 mgm./100 gm. cleared the blood temporarily but did not cure. In earlier, light infections, there were 3 cures among 10 animals treated with 10 mgm./100 gm.

[There are two small errors in the authors' references to earlier work. Weinman and Franz (this *Bulletin*, 1946, v. 43, 207) worked with melarsen oxide, not melarsen ; and Claessens (this *Bulletin*, 1947, v. 44, 49) reported on propamidine, not pentamidine.]

ii. The main burden of this contribution is to reduce the authors' previous estimate (see i above) of pentamidine's prophylactic powers. Further experiments, under the same conditions as above, showed that an oral dose of 10 mgm./kgm. confers complete protection for only 4 or 5 days in only about 15 per cent. of rats treated. *E. M. Lourie*

Launoy, L. & Chaboud, G., Mlle. Des actions curative et préventive du diamidino-diphénoxypentane sur les infections à *Trypanosoma equinum*. [**Curative and Prophylactic Action of Pentamidine in** *T. equinum* **Infections.**] *C. R. Soc. Biol.* 1948, Apr., v. 142, Nos. 7/8, 432–3.

Details are given of experiments in which pentamidine was shown to exercise curative and prophylactic effects against *T. equinum* in mice, rats and guinea-pigs. The trypanosome strain had been obtained from the Oswaldo Cruz Institute, Rio de Janeiro, in June 1947, but its previous history is not given.
E. M. Lourie

Vaughan-Jones, T. G. C. **A Short Survey of the Aims and Functions of the Game and Tsetse Control Department of Northern Rhodesia.** Reprinted from *Rhodes-Livingstone Inst. J.* 1948, 12 pp.

The author gives a general, readable account of problems of game, tsetse and fisheries and of the method which is being developed by the Government of Northern Rhodesia for handling them. The author is Director of the Department of Game and Tsetse Control in that territory.

The subject is in itself very complex, for in one place game may be an asset, in another a liability ; so that there are conflicting interests between conservation and development of the territory or between the sportsman or the protectionist on one side and the pastoral or agricultural African on the other. Moreover, different methods of studying the problems and dealing with them have been developed in different territories on the eastern side of Africa. It is certainly clear that it is wise to consider the whole of the wild life as a related group of problems, and that these are important economically, particularly in this large territory with a sparse population of people who are dependent to a great extent on food which they can themselves obtain or produce.

The Government of Northern Rhodesia started well by establishing the facts. They obtained the services of C. R. S. Pitman, who produced a faunal survey published in 1934. In it he not only set down a mass of information about the animals and their distribution in the territory, but he also defined the main problems and suggested methods for their solution, based on his own long experience in Uganda. Some of the immediate obvious problems are the control of elephant and of the ivory trade, and development of what is required by the tourist and the sportsman ; also the control of game in areas where it competes with cattle, the destruction of tsetse and the development of fisheries. The author in his position of Director of the Game and Tsetse Department of the territory has endeavoured to develop a unified view of these biological problems and a unified way of dealing with them. Here he has met with success, partly it is believed, because of his experience in administration in this country.

Two problems are of immediate concern to the readers of this *Bulletin*. The first is tsetse, mainly *G. morsitans*. The policy of the Department has been to take the diverse methods developed by neighbouring countries north and south, and to make use of game exclusion or destruction and also of selective clearing in places where there were urgent tsetse problems. As two methods have been used it is not possible to state which is most effective, but the general results are empirically encouraging. The second problem is the risk of spread of rinderpest from Tanganyika and countries to the north into the Rhodesias. This was met partly by control of movement of cattle but also by destruction of game along a line which was approximately the southern frontier of the distribution of the disease.

The general tone of the paper is discreetly optimistic. One receives an impression that the author has thought very carefully about his group of problems, that some success has been won against the tsetse and that the prospect of adding wealth to the country directly or indirectly is considerable.

P. A. Buxton

Tobie, Eleanor J. & Rees, C. W. **The Cultivation of *Trypanosoma cruzi* in Dialysate Medium.** [Research Notes.] *J. Parasitology*. 1948, Apr., v. 34, No. 2, 162–3, 1 fig.

This note describes a medium prepared in loops of Cellophane tubing by suspending them in the overlay of a diphasic blood agar medium which is used for the routine cultivation of the organism. The stock medium consists of a blood agar made essentially as recommended by Senekjie [this *Bulletin*, 1944, v. 41, 548] ; slants of this are overlaid with an equal quantity (10 cc.) of Locke's solution. For details of preparation and an illustration of the loop assembly the original paper should be consulted.

It is stated that *Trypanosoma cruzi* has been maintained in the dialysate medium for more than a year at a temperature of 24°–25°C. Bi-weekly serial transfers have been made from an inoculum of about one cc. of loop fluid containing active organisms : growth has been good and the viability of the organisms has not decreased.

It is concluded that *T. cruzi* may thus be grown without proteins or other non-dialysable substances. *H. J. O'D. Burke-Gaffney*

Dias, E., Laranja, F. S. & Nobrega, G. Clinica y terapeutica de la enfermedad de Chagas. [**Clinical Characters and Treatment of Chagas's Disease.**] *Medicina.* Mexico. 1948, June 10, v. 28, No. 557, 224–36.

Romaña, C. Profilaxis de la enfermedad de Chagas. Ideas generales sobre el Tema. [**Observations on the Prophylaxis of Chagas's Disease.**] *Bol. Oficina Sanitaria Pamamericana.* 1947, Nov.–Dec., v. 26, Nos. 11/12, 936–42. English summary.

Hauschka, T. S. & Goodwin, Margaret B. *Trypanosoma cruzi* **Endotoxin (KR) in the Treatment of Malignant Mouse Tumors.** *Science.* 1948, June 4, 600–602.

LEISHMANIASIS

Sen Gupta, P. C. **Observations on an Outbreak of Kala-Azar in Calcutta.** *Indian Med. Gaz.* 1947, Dec., v. 82, No. 12, 726–34, 5 graphs and 3 maps. [10 refs.]

In 1921, a kala azar out-patient clinic was opened at the Calcutta School of Tropical Medicine : at this clinic, data were collected which led to the observation, by Knowles, Napier and Das Gupta in 1923 [this *Bulletin*, 1923, v. 20, 866] that kala azar was highly endemic in one quarter in Calcutta, whereas much of the town was comparatively free of infection. Intensive investigation in this quarter by these workers led to the first incrimination of the sandfly *Phlebotomus argentipes*, which subsequent investigation, culminating in the work of Swaminath, Shortt and Anderson [*ibid.*, 1943, v. 40, 227] showed to be the vector.

This clinic has continued to operate, and in the years following the Bengal famine of 1943 an increase in the numbers and in the severity of the cases of kala azar was noted. Records of attendance of fresh cases show a rise to a high plateau in the years 1923, 1924 and 1925 (over 1,100 cases) with a gradual fall to 1930 (236 cases) and another increase in 1944 which culminated in a very sharp rise at the beginning of 1946. Distribution maps of indigenous cases in 1922–23 and 1942–43, respectively, show that little change occurred, but in 1946, although the old endemic area shows the greatest concentration of cases and the non-infected areas in the centre of the town are strikingly free still, there is a tendency for a centrifugal spread to the surburban areas that adjoin the endemic area. The increase in the severity of the disease is reflected in the frequency of complications, *e.g.*, from 1935 to 1939 the incidence of cancrum oris was 1·7 per cent. and from 1943 to 1946 7·1 per cent. ; and 5 cases of agranulocytosis occurred in 1946 and the first half of 1947, whereas this complication was not observed in Indian cases before 1942.

The factors which led to this increase were, the author considers, (i) the famine of 1943, at its worst from August to November, which caused widespread economic distress especially among the poorer sections of the population ; (ii) the increased incidence of other diseases, cholera, smallpox, typhoid and malaria ; (iii) the population factor, *i.e.*, the presence of susceptible material in the form of children born since the last epidemic wave ; and possibly (iv) an increase in the virulence of the parasite. " The indications are that, by the passage through this devitalized and highly susceptible population, the virulence

of the parasite was enhanced and the epidemic was maintained and progressed to the peak even when most of the other epidemiological factors had ceased to operate." *L. E. Napier*

CHANG, N. C. & HOU, T. C. **Cold Hemagglutinin in Chinese Kala Azar.** *Proc. Soc. Exper. Biol. & Med.* 1948, May, v. 68, No. 1, 72–4.

"Cold hemagglutinin in titers above 1 : 32 has been found in only 16·2% among 68 Chinese patients with kala azar. The highest titer obtained was 1 : 256. The titer bears no relationship to the severity, stage, and treatment of the disease. Our results further suggest that there is no correlation between cold hemagglutinin titer and serum globulin content."

SEN GUPTA, P. C., MALLIK, K. N. B. & CHAKRAVARTY, N. K. **Observations on Pneumococcal Meningitis as a Complication of Kala-Azar.** *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 8–11, 2 figs. on 1 pl.

The only reference to pneumococcal meningitis as a complication of kala azar that the authors were able to find was a statement by Rogers in his *Fevers in the Tropics* (1919) that he found two instances in a series of 40 post-mortem examinations in cases of kala azar.

The authors report four cases of kala azar in which a fatal pneumococcal meningitis occurred. The cases were encountered during the period of increased endemicity and increased severity of kala azar in Calcutta that followed the Bengal famine of 1943. All the patients were severely ill prior to the development of this fatal complication. In one case, it was secondary to pneumonia, in one to cancrum oris, and in one to otitis media ; in the fourth case no other focus was detected. All four patients were severely anaemic (haemoglobin, 4·67 to 6·18 gm. per 100 cc.) and all but one had marked leucopenia (1,300 to 2,000) ; the exception was the patient with pneumonia (24,000). The cerebrospinal fluid was under only slight pressure ; it was slightly hazy and not purulent ; and there were only scanty pneumococci present.

The treatment given was penicillin intrathecally and intramuscularly : there was no response, and the fatal issue—within 24 to 36 hours of onset of symptoms—was not postponed. It was considered that the leucopenia explained the relatively low cell counts in the cerebrospinal fluid and the rapid course of the disease. *L. E. Napier*

GHOSAL, S. M. & SINHA, Y. K. **Trial of Pentamidine Isothionate in Kala-Azar Cases in the Patna Medical College Hospital (Preliminary Report).** *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 11–14.

Treatment by pentamidine isethionate was undertaken in 20 cases of kala azar, in 10 of which the diagnosis had been made by the finding of parasites in the sternal puncture smear ; in the remainder the diagnosis was by the aldehyde test, which was positive in every case.

The injections were given on consecutive days, intramuscularly. The first dose was 1 ml., the second 1·5 ml. and the third and subsequent doses 2·0 ml. of a 10 per cent. solution. [The average weight of the patients was almost 100 lb., so that the average maximum dose was 2 mgm. per pound.]

The results were judged mainly on a clinical basis. The temperature fell to normal after 5 or 6 injections in all but 6 cases. The size of the spleen was diminished. The patient felt improved. There was an increase in body weight in 16 patients. The red cell count and haemoglobin improved. [It is however noted from the table that at the end of 10 days, although in most cases

improvement is recorded, no red cell count was over 4,100,000 and in 8 cases it is given as below 3,000,000. There are no records of leucocyte counts.]

The authors state that " No relapse was found in any of the cases so far observed ". [They do not state if there was any form of follow-up of cases. In the paper there is no evidence that any case was followed for more than a few weeks after completion of treatment. However, this paper is called a preliminary report, so that further information may be given later.]

There is no record of any ill-effects except bleeding from the needle track which was apparently troublesome in a few cases. [In the title and the text isethionate is spelt " isothionate ".] *L. E. Napier*

RANQUE, J., RANQUE, M., CABASSU, J. & CABASSU, H. Le diagnostic précoce de la leishmaniose canine par la ponction ganglionnaire. Réflexions à propos de soixante examens positifs obtenus en dix mois dans la région marseillaise. [**The Early Diagnosis of Canine Leishmaniasis by Gland Puncture : 60 Positive Results in Ten Months in the Marseilles Region.**] *Bull. Acad. Nat. Méd.* 1948, v. 112, Nos. 19/20, 339–40.

Gland puncture in dogs can be carried out on a large scale, it is easy to perform, is acceptable to dog-owners, gives a satisfactory percentage of positive results and allows a very early diagnosis of canine leishmaniasis to be made before the clinical manifestations are clear.

In 94 dogs examined in the Marseilles area in 10 months, only 40 were clinically suspicious of leishmaniasis, and 6 were completely asymptomatic. Gland puncture revealed 60 positive, 29 negative and 5 doubtful results. In 46 formol reactions carried out in parallel, only 15 were frankly positive, 30 were negative and one was doubtful. In two dogs, leishmania were found in skin smears and in four others they were found at autopsy in the bone marrow, liver and spleen. The full results will be published later, but the authors make the following observations :—

(1) Gland puncture gives the most significant results in the early stages of the disease, before the formal reaction or the clinical features are diagnostic.

(2) When the disease is established, the furfuraceous dermatitis and the positive formol reaction make the diagnosis simple : but leishmania are far fewer in the glands and prolonged search may be required before they are found : if gland punctures are persistently negative, resort is had to smears from the skin, marrow, liver or spleen.

(3) In the final stages, the leishmania seem to be lysed in the glands, liver and spleen, but persist intact in the bone marrow in large numbers.

(4) In 20 cases where a particularly early diagnosis was made by gland puncture, in the absence of any suspicious skin lesion, antimony treatment suddenly resulted in the appearance of the characteristic furfuraceous dermatitis and a spontaneous deterioration in the general condition : this new phenomenon is regarded as being analogous to the Herxheimer reaction in syphilis.

(5) Gland puncture has a prophylactic value, as it allows serial diagnoses to be made at the earliest stages when the disease is probably most contagious.

(6) Canine leishmaniasis is still as endemic around Marseilles as it was when PRINGAULT described it in 1914 [this *Bulletin*, 1914, v. 4, 398].

H. J. O'D. Burke-Gaffney

BOLLIGER, A. & BACKHOUSE, T. C. **Transmission of Kala-Azar to the Australian Marsupials** *Trichosurus vulpecula* **and** *Pseudocheirus laniginosus*. *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, May, v. 41, No. 6, 797–814, 14 figs. on 4 pls. [13 refs.]

In an earlier paper ARMYTAGE & BOLLIGER [this *Bulletin*, 1945, v. 42, 358] reported on their successful inoculation of *Leishmania donovani* to the pouch

young of the common Australian possum (*Trichosurus vulpecula*). In the present paper, a full account of further experiments with twenty-four possums and one ring-tailed possum *Pseudocheirus laniginosus* is given. Twenty-three of the twenty-five animals, including the ring-tailed possum, became definitely infected. The animals were of all ages. Pouched young remained longer in the pouch, up to 6 months instead of the usual 3 or 4 months, and showed stunted growth and fine grey woolly fur. The time of survival varied from 81 to 704 days. Some of the larger animals which survived infection for over a year showed no immediate effects of the infection for several months apart from a transient conjunctivitis and other eye changes. Loss of weight or failure of the growing animal to increase normally was one of the earlier signs of infection. The fur changed to a fine woolly structure. Occasionally necrotic skin lesions appeared temporarily near the root of the tail.

In the majority of possums serious eye changes occurred. Apart from the conjunctivitis, which cleared up after a few weeks or months, the cornea became hazy and iritis developed. The haziness was due to small whitish dots adhering to the posterior aspect of the cornea. Increasing keratitis giving the cornea a bluish-white opaque appearance might seriously or completely impair the sight. The iris showed a tendency to adhere to the lens. In some cases corneal abrasions scars and haemorrhage into the iris were noted.

Advanced kala azar produces marked degeneration of the testes. This is manifest by diminution in size and alteration in spermatogenesis. The testes may be only a half or a third of their normal size, while abnormal spermatozoa are produced or complete cessation of spermatogenesis may occur. In the majority of females, the pouch and mammary glands are found to atrophy. The pituitary and suprarenals were generally smaller than normal and frequently contained parasites so that the genital atrophy and stunted growth may have been caused by interference with the gonadotropins and growth hormones. In the brain and spinal cord the lesions take the form of a dense invasion of the pia-arachnoid with lymphoid cells, and perivascular infiltration in the cerebral cortex and grey matter of the cord. There is marked proliferation of adventitial cells around the cortical capillaries and many of them include parasites. In most animals the spleen is enlarged, but in three it was reduced in size. Generally the size of the liver fell within normal limits, though excessively large livers occurred as well as small ones. The kidneys appeared normal, but in half the animals parasitized cells occurred. In one animal parasites occurred in cells of the renal tubules. Parasites were present in all the organs after the single injection intraperitoneally or intracardially of blood from another infected animal, of culture or of bone marrow from a human case.

It is evident that the Australian marsupial, the possum, is highly susceptible to kala azar and will be a suitable animal for investigation of the disease in that country. The details of the history and histological findings in three of the cases are given, while the appearance of the abdominal organs of two cases are shown in photographs and histological findings are illustrated by twelve micrographs. *C. M. Wenyon*

HERTIG, M. & FAIRCHILD, G. B. **The Control of Phlebotomus in Peru with DDT.** *Amer. J. Trop. Med.* 1948, Mar., v. 28, No. 2, 207–30, 1 map & 4 figs. on 2 pls.

The authors, both of whom are authorities on the entomological side of the subject, give an account of the control of *Phlebotomus* in Peru with DDT, together with a number of valuable notes on the biology of these insects.

Preliminary work in the Mediterranean had shown that spraying houses with DDT in kerosene results in a very great reduction in nuisance from sandflies and

in the number of specimens of *Phlebotomus* which can be caught, though there was no reduction in untreated buildings in the neighbourhood.

The work here described was carried out in 1945 in Peru, a country in which *Phlebotomus* is of great importance as a vector of human disease. The authors worked in the Rimac Valley at a little over 6,000 ft. in places where *Phlebotomus verrucarum* predominated. They estimated the number of these insects by catching them in houses, stables, poultry houses, caves and cavities in stone walls, driving them out with tobacco smoke and observing them with an electric torch. They also estimated their abundance by the number of the characteristic bites on human beings, and by reports about annoyance from these insects. They also appear to have placed considerable reliance on what they describe as the " Burro rate " : we are inclined to suppose that this must refer to the number of sandflies biting a donkey (*Equus asinus*).

The authors' standard application was a 5 per cent. solution of DDT in kerosene sprayed at the rate of one gallon per thousand square feet on walls of houses, cavities in dry stone walls and so forth. The results are fully presented and discussed and are accompanied by photographs showing the type of building and of country, and plans showing which houses or walls were or were not sprayed in certain villages. It was found repeatedly that if a room or stable was adequately sprayed it was rare to find any sandflies or obtain any report of biting for several months : this, as the authors remark, would cover the whole sandfly season in many parts of the world. Even spraying the outside of a mud house is fairly effective and spraying the spaces in a dry stone wall is also effective. It seems then that with DDT applied in this way, one may not only suppose that a large number of sandflies are killed but one has a sort of barrier between the insect and the human inhabitants. The authors also point out that as the life cycle of *Phlebotomus* is long a sandfly population would only build itself up again very slowly after being greatly reduced by DDT [a point which one would like to see considered in relation to some population statistics]. As in other parts of the world, it was clear that the sandflies were flying a very short distance for they were discovered in numbers between 75 and 200 yards from the sprayed structures, provided suitable shelter was available. A point of interest in the present paper is that unlike much work on insecticides it pays very full attention to the biology of the insect.

The authors have also considered their results in relation to the spread of diseases transmitted by *Phlebotomus*. They controlled the insect in two large construction camps, and this was followed by an almost complete cessation of new cases of cutaneous leishmaniasis and bartonellosis. *P. A. Buxton*

FEVERS OF THE TYPHUS GROUP

GROENENDIJK, H. J. Die *Rickettsia prowazeki* im bebrüteten Hühnerei. [*Rickettsia prowazeki* **in Egg Culture.**] *Ztschr. f. Hyg. u. Infektionskr.* 1944, Nov. 12, v. 126, Nos. 1/2, 170–78.

GIROUD, P. & CIACCIO, G. Valeur de divers extraits pulmonaires de lapin infecté de *Rickettsia prowazeki*, jugée par l'agglutination des rickettsies. [**The Estimation by Rickettsia-Agglutination Tests of the Potency of Various Extracts of the Lungs of Rabbits inoculated with** *Rickettsia prowazeki*.] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 117–20. [10 refs.]

Soluble antigens were obtained from the lungs of rabbits infected with *Rickettsia prowazeki*, by extraction with ethyl alcohol, methyl alcohol, dilute glycerin, saline solutions, and distilled water.

The potency of the extracts was tested by inoculating rabbits with them and afterwards estimating the titre of complement-fixation tests carried out on the animals' serum.

The alcoholic extracts caused more rapid responses than the others, and when desiccated *in vacuo* at −40°C. retained their full antigenic power for at least 30 days. *John W. D. Megaw*

BIELING, R. & OELRICHS, Lilly. Untersuchungen über die Fleckfieberinfektion beim Kaninchen. [**Investigation of Typhus-Fever Infection in Rabbits.**] *Ztschr. f. Hyg. u. Infektionskr.* 1947, Jan. 6, v. 127, Nos. 1/2, 13–28.

This is a study of the reaction described by GIROUD [this *Bulletin*, 1938, v. 35, 790] as resulting from the intracutaneous injection of typhus rickettsiae into rabbits.

After a series of careful experiments the authors concluded that the intensity of the reaction in strictly controlled conditions could serve as a measure of the antigenic potency of suspensions containing living rickettsiae, and therefore also of the suitability of the suspensions for the preparation of vaccines. Yolk-sac material was regarded as suitable when it caused a definite reaction in dilutions of 1–10,000 to 1–100,000. With fresh suspensions the index of potency based on the reaction was parallel with the richness of the suspensions in rickettsiae.

With killed suspensions very rich in rickettsiae an early mild reaction occurred, owing to the presence of endotoxins; a similar reaction might also occur with living rickettsiae, but in this case it was followed by the more severe reaction resulting from the multiplication of the rickettsiae in the skin.

John W. D. Megaw

BIELING, R. & OELRICHS, Lilly. Untersuchungen über aktive und passive Fleckfieberimmunität bei Kaninchen. [**Investigation of Active and Passive Immunity against Typhus Fever in Rabbits.**] *Ztschr. f. Hyg. u. Infektionskr.* 1947, Jan. 6, v. 127, Nos. 1/2, 29–40.

Continuing their study of the Giroud reaction the authors found that a pronounced degree of active immunity against further intracutaneous inoculation with homologous rickettsiae was produced within seven days in rabbits which had been inoculated intracutaneously with large doses of yolk-sac suspensions containing living rickettsiae.

An appreciable degree of immunity was also caused by injections of killed suspensions, but often the immunity was not pronounced and the occurrence of allergic reactions due to the yolk-sac material was a source of fallacy, so that the reaction was not considered suitable for use in the practical testing of vaccines. Allergic reactions could, however, be prevented by using rickettsial suspensions of different origin for the second inoculation; for example, lung suspensions obtained from rabbits after several lung passages of infection; by this procedure all trace of the original yolk-sac material was removed.

The potency of rickettsial vaccines could be measured by finding the quantity of immune serum needed to prevent the occurrence of the Giroud reaction and then comparing this with the quantity of the same serum needed to prevent the reaction when a vaccine of known potency was employed in the same way.

John W. D. Megaw

SFORZA, M. Sul contenuto in agglutinine normali Antiproteus OX19 e OX2 in individui residenti in Eritrea. [**Agglutinins against *Proteus OX19* and *OX2* normally occurring among Residents in Eritrea.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 464–74. [11 refs.] English summary (7 lines).

Weil-Felix tests were carried out on groups of healthy persons in Eritrea before and after the epidemic of 1946. Before the epidemic season the percentage of reactions against *Proteus OX19* at titres of 1–160 and 1–320 were :— Among Italians 1·17, hill-country natives 8·2, and lowland natives 6·7. After the epidemic the corresponding figures were 13·2, 21·7 and 18·9.

Comparative tests with *Proteus OX2* were carried out only during the post-epidemic season ; titres higher than those observed with *OX19* occurred in 17 per cent. of the Italians, in 8 per cent. of the hill-country natives and in 18 per cent. of the lowland natives, so the reactions were mostly of the *OX19* type.

John W. D. Megaw

MORGAN, H. R., NEVA, F. A., FAHEY, R. J. & FINLAND, M. **Brill's Disease. Report of Two serologically proved Cases of Typhus Fever in Irish-Born Residents of Boston.** *New England J. of Med.* 1948, June 17, v. 238, No. 25, 871–3, 2 figs.

Two cases of typhus fever, serologically confirmed as being of the epidemic or louse-borne type, occurred in Boston in September 1946 and October 1947. The clinical features conformed to the pattern observed in Brill's disease.

Both of the patients had lived in County Galway, Ireland, till they emigrated to Boston, one in 1910 at the age of 20, the other in 1913, at the age of 17. In 1903 a serious epidemic of typhus fever occurred in County Galway when the patients were 13 and 7 years of age.

Complement-fixation and rickettsia-agglutination tests were carried out by Herald R. Cox and J. E. Smadel, both of whom regarded the results as diagnostic of epidemic typhus. In both cases the complement-fixation titres against epidemic antigen were two to eight times higher than those against murine antigen in the repeated tests that were carried out. The epidemic titre rose to 1–2,560 in each case. The results with the agglutination tests were less convincing, but when a difference in titre occurred the epidemic titre was always higher than the murine.

It appeared most likely that both of the patients had suffered from Brill's disease, the form of louse-borne typhus that occurs as a recrudescence of a latent infection persisting indefinitely after an attack of louse-borne typhus.

John W. D. Megaw

SCHMIEDER, F. Das Encephalogramm nach Fleckfieber. [**The Encephalogram after Typhus Fever.**] *Klin. Woch.* 1948, Jan. 1, v. 26, Nos. 1/2, 14–19, 12 figs.

The author describes the findings obtained by encephalography in 44 cases of after-effects of attacks of typhus fever which had occurred one to three years previously. The paper is illustrated by 12 excellent photographs.

The patients were not selected because of the special severity of their signs and symptoms ; their disabilities ranged from hemiplegia with pronounced psychosis to trivial neurological manifestations.

In two-thirds of the cases, some abnormality was detected ; this usually consisted in enlargement or deformity of the third ventricles. There was no definite correlation between the X-ray findings and the clinical features, but the author claims that the occurrence of an abnormality in the encephalogram

of a given patient increased the probability that his psychic or neurological defects had resulted from a previous attack of typhus fever. The procedure was therefore considered to be of diagnostic value.

In three cases it was found impossible to introduce air into the third ventricles, even after repeated attempts.

The author is doubtless justified in claiming that this is the first occasion on which encephalography has been employed in a systematic manner in the investigation of the persistent after-effects of typhus fever.

John W. D. Megaw

D'Ignazio, C. Il problema del dermotifo e della lotta contro il dermotifo in Etiopia (1936–1946). [**The Problem of Typhus Fever and its Control in Ethiopia (1936–1946).**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 423–9.

In this paper it is stated that the case-fatality rate of typhus fever (louse-borne) among Europeans in Ethiopia fell from 25–30 per cent. in 1937–1938, to 0·5 per cent. for the five years 1942–1946.

The causes of this astonishing fall are discussed, but even making the fullest allowance for early diagnosis, better methods of treatment, and a progressive decline in the virulence of the infection, the author feels compelled to fall back on the theory that the control measures, such as improvements in hygienic conditions, louse control, and the use of vaccines, have not only increased the resisting powers of the individual but also have produced a durable attenuation of the virulence of the rickettsiae through interference with the chain of transmission and adverse biological effects on the lice.

John W. D. Megaw

Davis, D. E. **Observations on Rats and Typhus Fever in San Antonio, Tex.** *Pub. Health Rep.* Wash. 1948, June 11, v. 63, No. 24, 783–90, 2 figs.

The author presents information on the composition of populations of rats (*R. rattus* and *R. norvegicus*) at San Antonio, Texas, and on the presence of typhus antibodies in them.

San Antonio lies about 30°N., that is to say outside the tropics. The climate is classed as "humid, sub-tropical." The average rainfall is 26·9 inches and rain generally falls in every month of the year. The mean temperatures over a series of years range from 63°F. in January to 84°F. in July and August.

The paper contains information on such matters as the length of head and body of the two species classified by sex and age, the criteria for age being based on the reproductive condition: also on the sex ratio of trapped and poisoned rats. It seems that reproduction occurs throughout the year with a maximum in the period May to June.

The presence of typhus antibodies was determined by complement fixation. In adult *R. rattus*, 34·7 per cent. were positive and in adult *R. norvegicus* 51·4 per cent. Rats from grain mills are more frequently positive than those from houses or stores and the difference is highly significant in a statistical sense.

P. A. Buxton

Savoor, S. R.; Vahia, N. S.; Soman, D. W. **Typhus in Bombay. Part I. Clinical Features** [Savoor, Vahia & Soman]. *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 20–24. [11 refs.] **Part II. Epidemiology** [Savoor, Soman & Vahia]. *Ibid.* 52–3.

During the years 1944 and 1945, more than 200 cases have been diagnosed as "endemic" flea-borne typhus on the strength of Weil-Felix reactions, presumably of the *Proteus OX19* type, at titres of 1–250 or over.

It was possible to study 70 of these cases at hospitals in Bombay City. The average duration of the fever was 12 days; a rash was seen in 24 per cent. of the cases, and the fatality rate was 2·8 per cent.

The incidence was greater in the first half of the year than in the second, there was a sudden drop in the number of cases in July and a further decline in August; flooding out of the rats by the monsoon rains was regarded as the probable cause of the low incidence during these months.

Five strains of rickettsiae were recovered from patients and another strain was recovered from one out of six rats captured in a house in which a case had occurred; a description of these strains will be given in a later paper.

No body lice were found on any of the hospital patients. The clinical and epidemiological features of the disease as described are consistent with the diagnosis of flea-borne typhus.

In an Appendix, a description is given of a new modification of the rapid slide test. The alcohol-killed suspensions of *Proteus OX19*, as supplied by the chief laboratories in India for the Weil-Felix test, are concentrated by keeping the bottles or ampoules in the ice-chest for five days and then removing the upper, relatively clear, two-thirds of the liquid with a pipette. To the remaining suspension a "small crystal" of sodium citrate and a drop of Loeffler's blue are added.

One drop of the suspension and a drop of the patient's blood are mixed on a slide which is gently rocked and a watch is kept for the occurrence of agglutination. The method was tested on 250 samples of blood whose Weil-Felix titres were known and it was found that clumping within ten seconds corresponded with titres of 1–500 or over; clumping within half a minute corresponded with a titre of 1–250, and within a minute with a titre of 1–125. When clumping was delayed beyond a minute, the result was of doubtful significance.

John W. D. Megaw

Fox, J. P. **The Long Persistence of *Rickettsia orientalis* in the Blood and Tissues of Infected Animals.** *J. Immunology*. 1948, June, v. 59, No. 2, 109–14. [15 refs.]

Rickettsia orientalis was recovered by mouse inoculation from the tissues of Swiss mice up to 610 days after experimental infection. Most of the mice had recovered from heavy doses of infection because of being treated with toluidine blue or methylene blue. The kidneys were the most infective organs, next came the brain and liver; the blood was less virulent because of the presence of antibodies. The urine was tested for infectivity on two occasions, with negative results.

Cotton rats were found to harbour infection in the blood and tissues up to the 102nd day after infection; the blood ceased to be infective by the 154th day, and the brain by the 269th, when the kidneys were still infective.

The author states that "the significance of these observations to the problem of the rodent reservoir in tsutsugamushi disease is obvious."

John W. D. Megaw

Noury, M. Sensibilité du mérion (*Meriones shawi* Lataste) au virus du typhus tropical. [**Susceptibility of the Rodent, *Meriones shawi*, to the Rickettsiae of Tropical [Mite-borne] Typhus.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 115–17.

A Moroccan rodent, *Meriones shawi*, was found to be at least as susceptible to intraperitoneal inoculation with *Rickettsia orientalis* as the closely related gerbille (*Gerbillus gerbillus*, *G. pyramidum*) which has been regarded as the animal of choice for experiments with the organism. *John W. D. Megaw*

SOMAN, D. W. & DAS MENON, V. K. **Scrub Typhus (Mite Typhus) in Bombay with a Report on the Isolation of Causal Rickettsia.** *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 17–20, 4 figs. on 1 pl.

Weil-Felix reactions of the *Proteus OXK* type were observed in sera from 16 among a large number of pyrexial patients in Bombay City during the year 1946. Rickettsiae were recovered by mouse inoculation from 8 of the 12 patients investigated. The organisms were similar to *Rickettsia orientalis* in their morphology, in the reactions produced in mice, and in the effects of intra-ocular inoculation of rabbits. There was also evidence of cross-immunity against a Ceylon strain of *R. orientalis*.

In 2 of the 12 patients an eschar was observed and in 6 there was a rash.

Fourteen of the 16 cases occurred in the months, September, October and November.

Special attention is called to the occurrence of scrub typhus in "even a metropolitan city like Bombay." [SAVOOR *et al.*, this *Bulletin*, 1948, v. 45, 781, has pointed out that contact with mite-infested vegetation is liable to occur in Bombay.] *John W. D. Megaw*

SFORZA, M. Dermotifo in Eritrea. (Identificazione dei virus storico, murino e da zecche). [**Typhus Fever in Eritrea. Identification of Epidemic, Murine, and Tick-borne Strains of Rickettsiae.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 430–32.

Details are given of the isolation and investigation of two strains of rickettsiae of epidemic typhus and of one strain of the murine type, but most of the paper is devoted to a description of a number of strains of tick-typhus infection.

Three of the tick-typhus strains were isolated from patients, three from ticks collected from dogs belonging to patients, and one from the brain of a dog which harboured infected ticks. The ticks concerned were *Rhipicephalus sanguineus* and *R. appendiculatus*. Two ticks of the former species obtained from an infected dog were allowed to feed on a guineapig, which in due course yielded a strain of rickettsiae.

Three strains of tick-typhus rickettsiae were thoroughly studied by passage through guineapigs and inoculation into the eyes of rabbits, each of them gave rise to cross immunity against the other two strains, but none immunized against epidemic or murine strains.

An outbreak of tick typhus is described in which ten persons living in a tick-infested area at an altitude of 888 metres were attacked; four of the patients had "inoculation" eschars. The Weil-Felix reactions were irregular; in most cases *Proteus OX19* gave a higher-titre reaction than *P. OX2*, but in one case there was an *OX2* reaction of 1–320 and a negative reaction with *OX19* and *OXK*, and in one case the *OXK* reaction was 1–160 as compared with reactions at 1–40 with the other two organisms.

The author concludes that the tick typhus of Eritrea is most closely related to boutonneuse fever; but it comes as a shock to be told that the causative organisms are "identifiable with *Rickettsia mooseri*." *John W. D. Megaw*

SFORZA, M. & SOLINAS, N. La reazione di Weil-Felix sul siero di sangue dei cani di Asmara. [**Weil-Felix Reactions in the Dogs of Asmara.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 475–82. English summary (8 lines).

Among 159 dogs captured at random in Asmara the following Weil-Felix titres were observed :—

	1–640	1–320	1–160	1–80	1–40	Negative
Against *Proteus OX19*	1	6	13	50	47	42
,, *Proteus OX2*	0	6	9	58	32	54

In the absence of reliable evidence the authors arbitrarily adopt a titre of 1–320 or over as evidence of the existence of rickettsial infection ; this is the same standard as has been adopted for human beings.

John W. D. Megaw

STREETEN, G. E. W., COHEN, R. S., GUTTERIDGE, N. M., WILMER, N. B., BROWN, H. E., SMITH, D. J. W. & DERRICK, E. H. **Tick Typhus in South Queensland : Report of Three Cases.** *Med. J. Australia.* 1948, Mar. 20, v. 1, No. 12, 372–3.

In two of the three cases described in this paper, there was a history of bite by a tick ten days or less before the onset of the fever. From the description given by the patients the tick was probably *Ixodes holocyclus*. In the third case there was no evidence of a bite but the patient had recently been walking in a " scrub area." In every case there was an eschar and lymphadenitis. The clinical features were consistent with the descriptions by ANDREW *et al.* of tick typhus in North Queensland [this *Bulletin*, 1947, v. 44, 202].

In one of the cases with a history of tick bite the Weil-Felix titres were *Proteus OX19*, 1–640 ; *P. OX2*, 1–320 ; and *P.OXK* negative. In the other case with tick bite the *OX2* reaction was not tested ; the *OX19* titre was 1–160 and the *OXK* reaction was negative. In the case without history of tick bite the *OX19* titre was 1–320 ; the *OX2* and *OXK* titre was 1–40.

The authors think it likely that in the past a number of cases of tick typhus have been regarded as murine typhus because of a positive reaction against *Proteus OX19*.

John W. D. Megaw

PAYZIN, S. & GOLEM, S. B. Türkiye'de Q hummasi. (Rapor I.) [**The Presence of Q Fever in Turkey.**] *Türk Ijlyen ve Tecrübi Blyolojl Derglsl.* Ankara. 1948, v. 8, No. 1, 94–113, 8 figs. on 4 pls. [12 refs.] English summary p. 116.

The authors inoculated 24 guineapigs intraperitoneally with blood from 16 patients who had clinical atypical pneumonia : 7 of the animals developed pyrexia and were killed and examined post-mortem ; their spleens were enlarged and *Rickettsia burneti* was recovered from them.

Complement fixation tests with Q fever antigen obtained from the Rocky Mountain Laboratory, were performed on 100 specimens of serum from patients having atypical pneumonia : 24 of these were positive at titres of 1/10 to 1/320.

Positive results were also obtained, however, in 13 of 115 sera sent for the Wassermann reaction (including 4 which also gave a positive W.R.), but the titre only exceeded 1/40 in one case.

Sixty specimens of serum from domestic animals were examined by the complement fixation test and 13 were positive.

The authors are pursuing the question of a possible relation between Q fever and contagious pleuro-pneumonia in goats.

H. J. O'D. Burke-Gaffney

LENGRAND, J. Nouvelle observation de Q fever faite dans les environs d'Alger. [**Another Case of Q Fever Observed in the Vicinity of Algiers.**] *Bull. Acad. Nat. Méd.* 1948, v. 132, Nos. 13/14, 251–3, 1 chart.

DE RODANICHE, Enid C. & RODANICHE, A. Fiebre "Q". Reporte de un caso y estudio del agente etiologico. [**Study of a Case of Q Fever.**] *Archivos Hospital Santo Tomas.* 1947, July–Dec., v. 2, Nos. 3/4, 327–48, 10 figs. [33 refs.]

ROSOVE, L., WEST, H. E. & BOWER, A. G. **Q Fever: Case treated with Streptomycin.** *Ann. Intern. Med.* 1948, June, v. 28, No. 6, 1187–92, 3 figs. [14 refs.]

"Q fever has recently been identified in the Artesia area of Los Angeles County. A case of Q fever is reported here with clinical and roentgenographic findings consistent with this diagnosis and confirmed by positive complement-fixation tests. Treatment with streptomycin was instituted and proved satisfactory, although further clinical investigation is necessary to establish its efficacy in this disease."

BLANC, G., BRUNEAU, J., POITROT, R. & DELAGE, B. Quelques données sur la Q fever (maladie de Derrick-Burnet) expérimentale. [**Some Findings in Experimental Q Fever.**] *Bull. Acad. Nat. Méd.* 1948, v. 132, Nos. 13/14, 243–50, 4 figs.

The authors describe the results of a considerable number of experiments, carried out primarily as a therapeutic measure, in which patients [presumably suffering from mental disease] were inoculated with the rickettsiae of Q fever.

Three strains of rickettsiae were used; two of these were from ticks found infected in Morocco and the U.S.A., the third was isolated from a patient in Athens. No significant difference was observed between the three strains. The routes of inoculation were intramuscular, intradermal, and respiratory. Some of the infecting suspensions were obtained from the spleens of guineapigs, others from ticks (*Rhipicephalus* or *Hyalomma* sp.).

Inoculation by the intramuscular route with spleen substance caused a short spell of fever lasting three to five days, with an incubation period of one or two days; the general symptoms were negligible, but the local reaction was pronounced. Rickettsiae could be isolated from the patients' blood.

Tick suspensions inoculated by the same route caused more prolonged fever, often of a two-phase type, but the general symptoms were trivial.

Intradermal injections of spleen substance were employed in ten cases; the only general reaction observed was slight fever in two; the local reaction lasted about ten days and "exceptionally" there was an eschar. Rickettsiae could be isolated from the blood in only one of the cases.

Instillation by the nasal route with a few drops of tick suspension was employed in six cases; the only result was a slight rise in temperature.

The only cases in which characteristic pulmonary signs occurred were two in which the patients were caused to inhale heavily infected suspensions administered by the aerosol apparatus and a mask; the two operators, though protected by masks, and two other persons who had been present at a distance of several yards, also became infected and developed pulmonary manifestations.

Even the symptomless attacks caused by intradermal inoculation produced a state of immunity.

Rickettsia-agglutination reactions at titres of 1–5 to 1–250 were observed in all the 22 cases in which tests were carried out. *John W. D. Megaw*

BIELING, R. & OELRICHS, L. Experimentelle Untersuchungen über die Infektion mit Rickettsia quintana (pediculi). [**Experimental Investigation of Infection with** *Rickettsia quintana* (*pediculi*).] *Ztschr. f. Hyg. u. Infektionskr.* 1947, Jan. 6, v. 127, Nos. 1/2, 41–8.

The authors found that suspensions of lice containing living *Rickettsia quintana* caused the Giroud intracutaneous reaction in rabbits, and that

homologous immune serum prevented the reaction, whereas anti-typhus serum had no inhibiting effect.

The homologous immune serum did not kill the rickettsiae ; these remained infective to lice after its application.

The serum of human convalescents from trench fever also inhibited the *R. quintana* intracutaneous reaction ; this observation forms the basis on which a practical test for trench fever can be developed. The serum of persons immunized by trench-fever vaccine had no pronounced inhibiting effect on the reaction. *John W. D. Megaw*

Bieling, R. & Oelrichs, Lilly. Beobachtungen über die Dauer der Infektion mit Rickettsia quintana (pediculi). [**Observations on the Duration of Infection with** *Rickettsia quintana* (*pediculi*).] *Ztschr. f. Hyg. u. Infektionskr.* 1947, Jan. 6, v. 127, Nos. 1/2, 49–53.

The authors mention that the American Trench Fever Commission appointed during the first world war found that the blood of trench-fever patients might remain infective up to 442 days after the onset of the attack.

The present observations were made on Russian prisoners of war employed as " donors " of blood to clean laboratory-bred lice which on several occasions became infected with *Rickettsia quintana* although the prisoners had not been exposed to any risk of infection for two or three years ; it was assumed that infection might possibly exist for much longer periods. The infectivity was not associated with recrudescences of the disease in recognizable form ; in some cases there were single spells of fever : in others there were two or more spells at long intervals, and after these trivial illnesses infectivity to lice might persist for several weeks. *John W. D. Megaw*

BARTONELLOSIS

Ricketts, W. E. **Intercurrent Infections of Carrion's Disease observed in Peru.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 437–51, 6 figs. [33 refs.]

[A paper of great interest and one to stimulate observation, for the findings are very definite though the number of cases on which they are based is comparatively small.]

Out of 105 cases of Carrión's disease, 50 were attacked by intercurrent infections. *Malaria* heads the list, as is only natural since the two diseases are endemic in the district where the investigation was carried out. The course of the bartonellosis did not seem to be affected by the malaria though the clinical features of both diseases might be modified. The sweating, splenomegaly and monocytosis present are due to the malaria. When the latter infection occurred in the pre-eruptive stage its course might be very atypical, the characteristic chills and fever might be absent.

Intestinal infections—including under this heading infections at first systemic, such as enteric fever and others of the group—were most serious. Of four patients with a complicating typhoid fever three died, as did both of two with *Salmonella paratyphi B* infection ; three others had what the author calls an " anaerobic intestinal septicaemia ", the organism not being identified, and all died. *Entamoeba histolytica* infection is another dangerous complication. The author saw three such and all ended fatally after an acute illness with high fever and symptoms generally like those of the *Salmonella* infection, and at autopsy multiple necrotic septic foci were found in the liver and spleen.

It is thought that *Bartonella* anaemia " predisposes fatally to septic invading organisms from the gastro-intestinal tract." *H. Harold Scott*

See also p. 884 HERTIG & FAIRCHILD, **The Control of Phlebotomus in Peru with DDT.**

YELLOW FEVER

WADDELL, Mary B. & KUMM, H. W. *Haemagogus capricornii* **Lutz as a Laboratory Vector of Yellow Fever.** *Amer. J. Trop. Med.* 1948, Mar., v. 28, No. 2, 247–52. [14 refs.]

Marmosets, *Callithrix jacchus* and a few *C. penicillata*, infected with a Brazilian strain isolated during an epidemic of jungle yellow fever, were used to test the capacity of *Haemagogus capricorni* to transmit yellow fever. The mosquitoes were allowed to become engorged on marmosets during the period when virus was circulating in the blood, and were then kept at 20° to 22°C. except for a period of four to five hours each week-day, when they were exposed to 30° to 31°C. The titre of virus in the marmosets was determined by experiments with mice. After an incubation period of fourteen days or longer, the mosquitoes were tested for infectivity by feeding them on baby mice, except in a few cases when marmosets were used.

The capacity of a given insect to transmit infection by bite was not constant. In general it was found that a concentration of virus in the circulation of $10^{7.0}$ or higher was necessary to produce infection in the mosquito, and negative results were obtained when marmosets were used containing concentrations of $10^{2.6}$ to $10^{5.6}$ of circulating virus in the blood. *E. Hindle*

LAEMMERT, H. W., Jr. **Studies on Susceptibility of Neotropical Rodents to Different Strains of Yellow Fever Virus.** *Amer. J. Trop. Med.* 1948, Mar., v. 28, No. 2, 231–46.

The susceptibility of various neotropical rodents to yellow fever virus has been investigated with the use of animals captured in various parts of Brazil inoculated with at least one pantropic strain of virus, including the African Azibi strain in its 39th to 43rd passage, and two South American strains, J.Z. and O.C., respectively. Some species were also tested against the French neurotropic strain. Three hundred and sixteen rodents belonging to twenty different species were tested, and the results are given in tabular form, showing those in which circulating virus was present and in addition those which developed neutralizing antibodies.

Coendou prehensilis, *C. paraguayensis*, *Dasyprocta aguti*, *D. aguti maraxica*, *D. azarae aurea*, *Akodon arviculoides* and *Sylvilagus brasiliensis* were resistant to all strains used. None circulated virus and, in general, the immunity response was poor.

The species belonging to the genera *Cercomys*, *Euryzygomatomys*, *Cavia*, *Nectomys* and *Oxymycterus* were also little susceptible and only a small percentage showed circulating virus.

Three species of *Proëchimys* tested gave quite different results. *P. cayennensis roberti* was found to be resistant ; *P. iheringi* sometimes showed circulating virus when inoculated with the Azibi strain but was resistant to two Brazilian strains ; *P. dimidiatus* could be infected with all three strains, but usually virus was present only in small amounts. Of three species of *Oryzomys* tested, *O. laticeps* circulated more virus than the other two, an unidentified species and *O. intermedius*.

Sciurus ingrami was found to circulate virus after inoculation with the Azibi and the J.Z. strains, but not with the O.C. strain. However, antibodies were developed against all three strains.

The large *Cuniculus paca* was the only species tested which invariably showed circulating virus after inoculation and developed neutralizing antibodies. These last two species also showed most virus in the blood stream, but the amount circulating was far below that appearing in certain infected primates.

Eight species were also tested against the French neurotropic strain but only one, *Nectomys squamipes* was found to be susceptible. *E. Hindle*

DENGUE AND ALLIED FEVERS

MELNICK, J. L. & PAUL, J. R. **Experimental Fort Bragg Fever (Pretibial Fever) in Chimpanzees.** *Proc. Soc. Exper. Biol. & Med.* 1948, Mar., v. 67, No. 3, 263–8, 1 fig.

This paper deals with a study of the filtrable virus of the short fever described by DANIELS and GRENNAN and called by them pretibial fever because of the frequent occurrence of a rash on the shins [see this *Bulletin*, 1944, v. 41, 278]. An exhaustive investigation by a team of experts failed to disclose the agent.

The virus was later isolated from a patient by TATLOCK, from whose description (*J. Clin. Investigation*, 1947, v. 26, 287) the authors quote in stating that it is lethal to hamsters and causes fever in guineapigs and rabbits. Tatlock is also quoted as stating that the strain was maintained through 23 serial passages in embryonated eggs and then successfully inoculated into 14 human volunteers, most of whom developed a short spell of fever lasting one or two days, and in " some " of whom there was a pretibial rash.

In the present study the strain of virus employed was received from Tatlock ; it was maintained by transmission through hamsters and was found liable to deterioration even when stored at a temperature of —70°C.

Brain suspensions from infected hamsters, when inoculated into a chimpanzee by combined intracutaneous, subcutaneous, and intramuscular routes, caused a characteristic attack of pretibial fever ; the incubation period was 10 days ; the fever lasted about two days ; there was a raised erythematous patch on the right shin and another on the left forearm ; blood taken during the spell of fever and inoculated by the same routes into another chimpanzee gave rise to the formation of neutralizing antibodies, but the animal was refractory and its temperature could not be taken. The first chimpanzee also developed neutralizing antibodies and was found immune when challenged with a further dose of the virus.

Two other chimpanzees developed short febrile attacks after inoculation, and from one of them the virus was transmitted to hamsters by blood inoculation ; in both of them, and also in a fifth chimpanzee, whose temperature could not be taken, the presence of antibodies was demonstrated.

Large numbers of hamsters were used for testing the activity of the virus and for the detection of neutralizing antibodies.

Four rhesus monkeys were inoculated with suspensions which were lethal to hamsters, but the results were entirely negative. *John W. D. Megaw*

PLAGUE

MEYER, K. F. & FOSTER, L. E. **Measurement of Protective Serum Antibodies in Human Volunteers inoculated with Plague Prophylactics.** Reprinted from *Stanford Med. Bull.* 1948, Feb., v. 6, No. 1, 75–9.

It is not sufficient to establish the bare fact of efficient immunization, and the need remains in many infective diseases to determine its degree and duration. "Agglutination tests, complement fixation tests and whole blood tests have all proved inadequate." A test known as the "mouse protection" test is in use now for the measurement of degree of passive immunity in yellow fever, typhoid fever and dysentery. The authors apply this to the case of plague and use a subcutaneous infective challenge dose of 2,000 *P. pestis* organisms in 0·2 ml. broth, equal to 100 MLD. The test mice were of uniformly susceptible ABC inbred strain and each received 0·5 ml. undiluted immune serum from human volunteers intravenously. The volunteers were separated into 4 groups of 10 each, according to the nature of their prophylactic inoculation :—I. Army prophylactic, 3 injections, 7 billion formalin-killed; II. Fraction I antigen, 2·5 mgm. in 3 doses; III. One injection of 1,000 million avirulent No. 1122; and IV. One injection of 1,000 million avirulent "Tjiwidej." As "the differences, first in percentages of mortality, and second in the length of survival time, are not strikingly significant when considered separately; but when the two factors are considered together, the results of the test become significant," the authors unite the two factors in a "protection index," the percentage mortality divided by the average time of death.

Conclusions drawn are briefly :—1. Administration of purified Fraction I plague antigen [this *Bulletin*, 1947, v. 44, 712] "to non-immune human volunteers results in the production of large quantities of protective antibodies in the blood. Formalin-killed virulent plague bacilli and one strain (No. 1122) of living avirulent bacilli are decidedly less effective. The well-known strain 'Tjiwidej' as used in these studies proved non-immunogenic." 2. Adequate protection requires reinoculation and this stimulates a higher level of antibodies than the primary inoculation, but some individuals fail to react to these "booster" antigenic doses. *W. F. Harvey*

CHOLERA

TEUBER, Ilse. Die Cholera in der Schweiz. [**Cholera in Switzerland.**] *Ztschr. f. Hyg. u. Infektionskr.* 1947, Jan. 6, v. 127, Nos. 1/2, 166–84, 5 figs. [24 refs.] A historical review.

RAO, S. R. **Role of *Palkies* (Moving Religious Fairs) in the Epidemiology of Cholera with special reference to Sri Eknath Maharaj *Palki*.** *Indian Med. Gaz.* 1947, Dec., v. 82, No. 12, 746–50.

Pilgrimages and shrines in India and Arabia have been, epidemiologically, associated with cholera outbreaks. In the case of the present pilgrimage along a route of over 300 miles traversed on foot, we have an instance of a miniature pilgrimage during which a cholera epidemic might have, but did not, take place. It is a common custom for a palanquin or *palki*, carrying the sandals of a saint, to be the centre of the procession. Pilgrims start with the palki and obtain fresh accessions en route; in the same way pilgrims disperse

or arrive back on the return journey. Cholera cases may be occurring at the commencement of the journey, may be present in villages on the way, and may be brought back again from the shrine of attendance. This pilgrimage started in 1941 " from Patan a town heavily infected with cholera " and came under the author's control only with its arrival within the dominions of the Nizam of Hyderabad. He had it under supervision both going and coming within the State and it swelled at one time to as many as 1,500 persons. An occasional case of cholera required attention on the outward journey, but in none of the cases did it spread, while on the return of the palki, with nearly 1,100 pilgrims, not a case occurred. The precautions adopted were compulsory (indirect) inoculation of all pilgrims, treatment of wells with permanganate or bleaching powder, and great care over the feeding of the pilgrims, which was the obligation of villagers *en route*. Inoculation is called compulsory and indirect because no pilgrim was allowed to join who had not been vaccinated. It is reasonable to claim that these precautions prevented the outbreak of cholera among the pilgrims themselves and among uninfected villages, through which they passed or to which they gave off their fellow pilgrims. *W. F. Harvey*

Gohar, M. A., Elyan, A., Makkawi, M., Eissa, A. & Bashatly, A. **The Viability of Pathogenic Intestinal Organisms in Sea Water with special reference to** *Vibrio cholerae*. *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 358–72, 3 maps.

It seems certain that all coastal sea water into which local sewage is discharged will be in greater or less degree diluted sewage. The viability of an organism like that which is designated the " true " cholera vibrio is important. Earlier work, done at a time when selection had not established the definition of the cholera vibrio in its narrowest sense, gives little help in solution of the problem. The authors have contributed direct data relating to the recent cholera epidemic in Egypt. Samples of water from several Egyptian ports with beach lines on the Mediterranean, the Nile, at the entrance of the Suez Canal and at Suez were artificially contaminated with 5,000 million cholera vibrios per litre and kept at a temperature of about 18°C., with the intention of testing them daily for viable cholera organisms. The cholera vibrio, however, disappeared from all the samples in about 24 hours : this could be interpreted as due to the overgrowth of hardier organisms or to the presence of an antibacterial substance in sea water. The next step was to try the samples out after getting rid of other organisms first by sterilizing, by adjustment of *p*H, and by making up a synthetic sample of sea water. The result of this trial showed that " the life of the organism is very short only in the filtered water which probably contains an anti-bacterial agent and is much longer in the autoclaved samples ". Filtration was through Seitz filters and autoclaving probably destroyed not only existent organisms, but also the hypothetical antibacterial substance. Viability of the cholera vibrio was especially long after adjustment of *p*H to suit its requirements. Other experiments were carried out for organisms other than the cholera vibrio and are pertinent to the disposal of sewage generally by discharge into coastal sea water. The remarks towards the end of the article sum up the position further :—" From the point of view of bathing and frequenting seaside resorts the danger of discharging sewage into the sea is overestimated. The main risk of infection with pathogenic intestinal organisms in the sewage seems to lie not so much in the contamination of the water itself as in the contamination of shell-fish ". Aesthetic reasons may, of course, be an important consideration in a coastal area for the imposition of regulations relating to the discharge of sewage. *W. F. Harvey*

BURROWS, W. & HAVENS, Isabelle. **Studies on Immunity to Asiatic Cholera. V. The Absorption of Immune Globulin from the Bowel and its Excretion in the Urine and Feces of Experimental Animals and Human Volunteers.** *J. Infect. Dis.* 1948, May–June, v. 82, No. 3, 231–50, 12 figs. [16 refs.]

A preceding study, IV, has already been abstracted [this *Bulletin*, 1948, v. 45, 335] and indicated that immune coproglobulin, indistinguishable from immune serum globulin, was present in the faeces of previously immunized guineapigs that had received experimental enteric infection with the cholera vibrio. The present study continues the research into the origin of the faecal antibody; whether it might be derived from seepage of serum antibody or direct from antibody-forming cells of the lymph follicles of the intestine; the permeability of the intestine to a large globulin molecule; and the behaviour of homologous and heterologous globulin in the passively immunized animal. The conclusions to the detailed experimentation are shortly :—1. " Immune globulin, immunologically indistinguishable from serum globulin, is excreted in the faeces and urine of actively immunized guineapigs and human volunteers ": it is independent of serum antibody and therefore is not derived from it. 2. Serum globulin is excreted normally in urine and faeces and immune globulin of immunized guineapigs is a partial substitution for normal globulin in the excreta. 3. Antibody appears in the faeces and urine of guineapigs passively immunized with homologous or heterologous antiserum. 4. " Homologous and heterologous immune globulin administered to the guineapig by intragastric inoculation is absorbed in large amount directly from the bowel without modification of its immunological properties " and it is evident that the immune globulin can readily pass in either direction through the bowel wall.

W. F. Harvey

SAFWAT, Y. & ADHAM, I. **Fluid Balance in Cholera.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 300–308.

Depletion of water and depletion of salt cause the most serious symptoms in cholera. Dehydration requires urgent and immediate treatment, but this treatment should be followed by a careful analysis as to how far the alteration in fluid balance is due to pure water depletion or pure salt depletion respectively. " Cholera presents a combination of the picture of both pure water and pure salt depletion ". As a result of pure water loss, tissue fluid and blood plasma become hypertonic and water is withdrawn from cells. With salt depletion the reverse takes place and tissue fluid become hypotonic. As the kidneys excrete water in an endeavour to maintain tonicity, the volume of tissue fluid decreases. The clinical picture differs when water depletion is set against salt depletion :—thirst contrasts with no thirst; diminution of urinary volume, with no diminution; no diminution of plasma volume, with marked reduction of plasma volume; no reduction of blood chlorides with reduction in blood chlorides and their absence from the urine. Circulatory changes are due to haemo-concentration and lowering of blood pressure. This differentiation of conditions demands specific treatment. " In simple water depletion patients require water and water only until the deficit has been replaced . . . . In pure salt depletion normal saline (0·85 per cent.) might be given . . . till the relief of symptoms ". Treatment then in cholera for the correction of the negative balance is :—(1) Estimation of haemo-concentration and administration of 400 cc. of normal saline for every rise of one degree of specific gravity of the blood above 1060. (2) Correction of any tendency to reversion to a negative reaction in the balance by increasing intake of water by the mouth. In the later cases investigated, parenteral administration of saline replaced continuous

intravenous saline, till the specific gravity dropped to 1060, after which it was sufficient to make the patient drink plenty of fluid. As there is usually reduction in the alkali reserve and tendency to acidosis, intravenous 4 per cent. sodium bicarbonate is recommended. The work of MARRIOT [this *Bulletin*, 1948, v. 45, 208] has greatly clarified the symptomatology of cholera. *W. F. Harvey*

SAFWAT, Y. & ADHAM, I. **Uraemia in Cholera.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 309–21.

A reference is made to the findings of CHATTERJEE and SARKAR [this *Bulletin*, 1941, v. 38, 583] which are summarized and which had led those authors to conclude that uraemia in cholera was not due to any structural change in the kidney, but that the cause was extra-renal and pre-renal. Safwat and Adham's own observations tend to confirm this view, and briefly are :—(1) Initially all cases had albuminuria which disappeared with recovery of renal excretory function and drop in blood urea ; oliguria changed to polyuria, even though blood urea was still high ; the specific gravity of the urine was low, and began to rise only when blood urea became normal ; casts were sometimes found and a low urinary chloride increased with improvement of the case and with drop in blood urea. (2) Blood uric acid, blood creatinine and blood urea clearance were highly correlated with blood urea values, positively, or negatively. Little evidence was found, from estimation of blood chlorides, of hypochloraemia. All the results pointed to a marked acidosis initially and gradual attainment of normality with general improvement and with treatment. Clinically the symptoms in cholera were those of dehydration, and symptoms of uraemia were slight even with very high blood urea.

" In other words there was a picture of renal failure developing acutely, coming to a maximum and finally, in the majority of cases, resolving completely in a short time ".

Structural changes in the kidney having been excluded as a cause for pre-renal azotaemia there remained the question of the mechanism of the impairment of renal function. Four factors are considered :—hypochloraemia, low blood pressure, disturbance of acid-base balance and nephritis due to toxaemia. The first and last of these explanations are rejected and leave the remaining factors as the explanation of symptoms and high blood urea in cholera.

W. F. Harvey

AWNY, A. **Some Haematological Aspects of Cholera Infection.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 351–7.

The author, in Cairo, studied the following haematological aspects of cholera : (1) the degree of haemoconcentration, (2) the leucocytic reaction, (3) the erythrocyte sedimentation rate, (4) the erythrocyte fragility.

The degree of haemoconcentration varied widely : the specific gravity of the blood was between 1056 and 1078 and the volume of packed red cells was from 48 to 80 per cent. ; haemoglobin varied from 85 to 135 per cent. and the highest figure for red cells was 7,500,000 per cmm. The author found that in almost every case these four data gave a fairly reasonable indication of the degree of haemoconcentration and correlated closely with clinical findings : but they had no prognostic significance. The constitution of the plasma also reflected the dehydration : in 18 of 25 cases the plasma specific gravity was above 1030 and in 21 of 25 the plasma protein concentration was 8 gm. per cent. or more.

Leucocytosis of 20,000 to 30,000 per cmm. was quite common, and this increase could not be explained solely on the basis of haemoconcentration.

The polymorphonuclear leucocytes were mainly involved and they also showed some left shift. The total leucocyte counts remained high (average about 12,000 per cmm.) after the acute stage was over and the dehydration had been corrected and even during convalescence: at this last stage eosinophiles characteristically increased and the author suggests that this point should be investigated further.

The erythrocyte sedimentation rate was estimated in 13 cases before and in 11 after rehydration treatment. The Wintrobe technique was used and corrected by haematocrit readings. Before treatment, the corrected E.S.R. range was 0·45 to 1·7 mm./minute (average 0·7 mm.) and after complete rehydration it was 0·6 to 1·5 mm./minute (average 1·0 mm.). The normal reading is 0·1 to 0·3 mm./minute by this method. It is suggested that the higher viscosity of the blood before rehydration interfered with the sedimentation rate. The corrected E.S.R. range in 9 patients during convalescence was 0·25 mm./minute to 0·6 mm./minute (average 0·45 mm.)

The finding of an increased E.S.R. during the acute stage of cholera and for some time afterwards differs from that of the " Indian workers " [not specified] and the discrepancy is attributed by the author to his having corrected the results by haematocrit readings, which he regards as essential.

Increased erythrocyte fragility during the acute stage of the disease was found in 13 of 14 patients when the Sanford technique (diminishing dilutions of NaCl solution) was used and in 6 patients tested by the Wiseman method (increasing dilutions of serum with distilled water). In the latter 6 patients, the icterus index was also high (12 to 23 units) in the acute stage, but fell to less than 8 units during convalescence. The author discusses the causes of the increased fragility. He believes, and quotes experimental evidence to support his belief, that in addition to the cholera toxin itself deficient capillary circulation tends to increase red cell fragility: probably trauma of the cells from marked dehydration and increased blood viscosity may also contribute to the fragility. He suggests that the icterus index is increased as a result of increased phagocytosis of the fragile erythrocytes by reticulo-endothelial cells; this would be favoured by stagnation of blood because of deficient and slow circulation.

H. J. O'D. Burke-Gaffney

El-Ramli, A. H. **Clinical Study of 689 Cases of Cholera isolated in the Abbassia Fever Hospital.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 322–50.

It must have been a trying experience for a medical man " with no previous experience of cholera " to take charge of a large and sudden serious epidemic, even though it also made sudden disappearance. Excellent details are given of this experience, which present a vivid picture of the cholera patient. Diarrhoea, vomiting and dehydration effects make up the symptoms. The diarrhoea is painless and the vomiting is unaccompanied by nausea. One has always been accustomed to associate colourless " rice-water " stools with cholera and it is interesting to note that the colour is first faecal, becomes colourless and then with the improvement of diarrhoea the stool becomes coloured, semisolid and solid as bile returns. Degree of dehydration was measured by the copper sulphate method for specific gravity of whole blood, which ranged from 1050 to 1078 in different cases. Blood pressure might be so low that it could not be taken at all, " or else a very low (70 or less) systolic pressure and no measurable diastolic pressure were found ". Fever was seldom present and infrequent symptoms were: hiccough, headache, oliguria, anuria, and abdominal colic. It was found that the concentration of blood urea, an early feature in cholera, " is not related at all to the haemoconcentration."

Similarly there was seldom any correlation between "blood chlorides and blood urea in the sense that as the blood urea decreased, the chlorides increased". Of complications, high blood urea concentration was the most common. In fact "it should be considered as a symptom and not as a complication" of cholera. Only a minority of these cases showed uraemia and that carried a grave prognosis.

The carrier and contact questions are answered in the data that 50, 91·7 and 100 per cent. of carriers were free of vibrios after the first 5, 10 and 15 days respectively. Contacts numbered 2,035 and the number of healthy carriers among them was 84, none of whom showed any signs of gastro-intestinal illness. Cholera rarely developed among contacts. Pathological findings in necropsies and histology are described and finally treatment is critically considered:—Treatment should be started as early as possible and it must be recognized that "the immediate danger to life is due to dehydration and circulatory failure". It is quite sufficient to give fluids by the mouth in patients with blood specific gravities up to 1060, and 400 ml. of normal salt solution should be given intravenously for each degree above that figure, firstly at 2–5 litres an hour and then at a slower rate. Acidosis was combated with "the addition of 40 gm. sodium bicarbonate to every litre of normal sodium chloride solution", which was passed through a Seitz filter. Digitalis was the heart stimulant used and sulphonamide drugs produced no effect on the course of the illness or on the case mortality. *W. F. Harvey*

GOHAR, M. A. **Vaccination against Cholera by a One Dose Method.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 373–6.

The great advantage, administratively, of a single-dose system for mass vaccination is obvious, even though it be proved that a two-dose system is much superior for real protection. In fact it may be that the first dose is more a sensitizing one for the following protecting dose than an immunizing one. An effort has been made by the author to combine the necessary properties of sensitization and immunization in a single dose by using an alum-precipitated cholera endotoxoid vaccine. His basic, 72-hour, broth culture containing 7,000 million organisms per ml. was really a mixture of intact cholera vibrios and endotoxin liberated by unstable thermolabile autolysin. This was "treated with 0·6 per cent. formalin, incubated at 37°C. for a week and then precipitated with 0·5 per cent. alum." The precipitate was resuspended in phenol saline and used as vaccine in mice. A challenging test dose, LD_{100}, was given intraperitoneally 10 days later. The survival results were compared in mice treated as follows:—one-dose heat-killed vaccine, two-dose heat-killed vaccine and an unvaccinated control series. These results were: 40 per cent. survival for alum precipitated vaccine, 45 per cent. for two-dose heat-killed vaccine and no survivals in the control. The result with the alum vaccine are sufficiently close to the heat-killed vaccine to suggest its effectiveness on a single-dose system. The object was to slow down the absorption of the single dose and so obtain its real immunizing potency. Slowness of absorption was indicated in man by injection intradermally, when the vaccine produced an indurated mass which persisted for a long time. If the "full dose was given by the subcutaneous route the general reaction was somewhat severe."

W. F. Harvey

KORDI, A. H. **Some Observations on the Effect of Cholera Vaccine during the Recent Cholera Epidemic in Egypt.** *J. Roy. Egyptian Med. Ass.* 1948, Apr., v. 31, No. 4, 289–99, 1 graph.

An endeavour has been made to obtain useful statistical data on the value of cholera vaccination. The variables are many and the investigation was

carried out on a hospital population, thus restricting it to incidence and fatality in previously vaccinated and non-vaccinated patients. Total admissions to hospital were 430 patients. Out of 281 non-vaccinated patients 69 died, while out of 149 vaccinated 14 died :—a result in favour of the vaccinated. Other data relate to the decrease in incidence and death rate with the lapse of time following inoculation and to the relative value of a single or a double dose of vaccine. Fatality rate was 9·81 per cent. in patients vaccinated with a single dose, 8·10 with a double dose and 24·55 per cent. in the non-vaccinated. The carrier question was taken up to determine the duration of excretion of vibrios in convalescent and healthy contact carriers, with the finding of a maximum period in the former of 33 days and in the latter of 15 days. One of the conclusions drawn is that vaccination not only afforded " a definite degree of protection but also lowers the fatality rate." *W. F. Harvey*

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS

Faust, E. C., Lewis, Ruth, Heilbrunn, Ilse, Hickman, Mary L. M. & Everritt, Martha G. Posibles determinantes de la patogenicidad de la *Endamoeba histolytica*. 1. Estudio de sus asociaciones bacterianas y su susceptibilidad a los antibióticos. [**Influences determining the Pathogenicity of *Entamoeba histolytica*. I. Study of the Bacterial Associations and their Susceptibility to Antibiotics.**] *Medicina*. Mexico. 1948, May 25, v. 28, No. 556, 206–10.

[This is a translation of a paper delivered at a Medical Congress in Mexico. It deals with a subject of the highest importance.] That the growth of *E. histolytica* is influenced by associated organisms is well known and the varied effects of the infection in man may be due to the nature of these organisms. The authors have investigated the bacteria associated with 21 strains of the amoeba, 18 already known, isolated or recorded by Faust, and three fresh strains. In 12 cases the species of bacterium present has been determined ; they were mostly Gram-positive cocci and Gram-negative, non-pathogenic bacteria of the coliform type. By means of antibiotics, penicillin and streptomycin, and by sulphadiazine, in amounts insufficient to harm the entamoeba, the organisms were removed from the growths. The resistance of the bacteria varied greatly ; some yielded readily, some needed relatively strong concentrations, some were quite unaffected. It was observed that the trophozoites might resist the action of high concentrations of penicillin and streptomycin for several hours and later develop well in the tubes containing an organism designated " T ". The early sterility and later development are attributed to late growth of sporing bacilli, inhibited in the early stage, or, secondly, to the presence of the antibiotic until diluted sufficiently in the course of experimental re-sowing, or, thirdly, to faulty technique. The first is thought the most probable.

Tests are to be carried out on susceptible animals with the entamoeba and with known isolated bacteria. [The paper is not easy to follow, as reference is made to several tables (*cuadro*) which have not been included in the present text.] *H. Harold Scott*

ALLAART, P. J. Een perinephritisch "amoebenabsces". [**A Perinephric 'Amoebic Abscess'.**] *Nederl. Tijdschr. v. Geneesk.* 1948, June 26, v. 92 (ii), No. 26, 1938–9.

The English summary appended to the paper is as follows :—

"A perinephritic abscess is described, which was caused by perforation of an ulcer in the colon ascendens in chronic amoebic dysentery."

ANDERSON, H. H., JOHNSTONE, H. G., PACKER, H., YOUNG, J. D., CALLISON, M. K., HAMBLY, A. S., Jr., ANDERSON, Jeanette Van D. & REED, Racheal K. **Incidence and Control of Amebiasis and other Intestinal Protozoan Infections in a Memphis Hospital.** *Amer. J. Trop. Med.* 1948, May, v. 28, No. 3, 373–82.

Previous surveys have shown the incidence of amoebiasis to range from 6·8 per cent. to 15·9 per cent. in various parts of the United States. The authors, working in an institution serving areas of Tennessee, Mississippi and Arkansas, confirmed the previous impression that amoebiasis is not predominently a disease of the South-eastern States of the Union. A systematic survey of the intestinal protozoal infection-rates in various groups of hospital patients was undertaken at Memphis, and an effort was made to appraise the rôle of *Entamoeba histolytica* in the causation of illness. Six specimens of stool, when procurable, were examined from each individual, and cases supplying less than three specimens were excluded from the records. The diagnosis was based on the examination of fresh and of iodine-stained wet preparations, and by the use of slides stained with Heidenhain's iron-alum-haematoxylin technique. Proctoscopy was done on all hospitalized patients proved or suspected to harbour *E. histolytica*. Among 246 persons adequately examined 42 (17 per cent.) were found to harbour *E. histolytica* ; the other commoner intestinal protozoa [with the exception of *Iodamoeba bütschlii* and *Trichomonas hominis*] were found in the usual ratios. The figure for *Entamoeba histolytica* infection was higher than expected and suggests that amoebiasis is more prevalent than was suspected fifteen years ago in the area. Of the 42 patients only 4 had dysentery ; one was an ex-serviceman, the only ex-service case examined, who had a history of relapsing amoebic dysentery dating from service in Burma ; another was a child of two years, who also suffered from clinical dysentery and was the only infected member of his family. At least half the patients were undernourished ; most gave a history of intestinal disorder ; and in the 26 proctoscoped all but 5 showed bowel changes.

Previous reports [this *Bulletin*, 1947, v. 44, 819] suggested that the thioarsenites C.C. Nos. 914 and 1037, dithiocarboxymethyl and dithiocarboxyphenyl derivatives of carbarsone oxide (C.C. No. 606) (carbamidophenylarsenous oxide) were ten times as active as carbarsone or as emetine *in vitro* against *E. histolytica*, and that they were similarly more active *in vivo* against experimental infections in *Macacus rhesus*. These drugs each were given in varying dosage by the mouth, and in the case of the second rectally, to series of infected patients. The results are tabulated. Oral dosage ranged from 3·0 gm. to 7·2 gm. over 7 to 24 days ; the rectal dosage was from 3 to 6 gm. over 6 days.

All but two of the patients were cleared of their *histolytica* infections by one or other of the courses. The drugs in some cases caused vomiting, but salol coating of the tablets obviated this. There was no evidence of systemic intoxication attending their use.

Fourteen patients infected with *Giardia intestinalis* were given chloroquine, 2·2 mgm. per kilo, orally for seven days. Three only were cured of the infestation. *A. R. D. Adams*

KLATSKIN, G. & FRIEDMAN, H. **Emetine Toxicity in Man: Studies on the Nature of Early Toxic Manifestations, their relation to the Dose Level and their Significance in determining Safe Dosage.** *Ann. Intern. Med.* 1948, May, v. 28, No. 5, 892–915, 2 figs. [57 refs.]

Emetine is necessary in the treatment of amoebiasis, but fear of toxicity has led to its employment in ineffective dosage. With reasonable care, moderate to large doses may safely be given. The early minor manifestations of emetine poisoning in man have received inadequate attention; the authors have re-studied these in 93 patients in a U.S. Army hospital. All the patients were confined to bed under close observation during the investigation; particular attention was paid to the blood pressure and the pulse rate, and electrocardiogram readings were taken before and during treatment at intervals of three days. The amounts of emetine given ranged from 1 to 27 grains, and the drug was given hypodermically, intramuscularly, or intravenously.

In 91 per cent. of the 93 patients there was some evidence of emetine toxicity; the symptoms encountered fell into four categories; local, gastro-intestinal, cardiovascular, and neuro-muscular. The side-effects were multiple in 70 per cent. of the patients; in 21 per cent. they were limited to one system. The local reaction to the drug was one of the most troublesome; it may be less if the injection is subcutaneous rather than intramuscular. Intravenously emetine did not prove more toxic, though transient immediate reactions were more frequent. The theoretical objections to intravenous medication are based on the sudden deaths due to ventricular fibrillation which have been seen in experimental animals. Such accidents have not been reported in man, but are potential hazards which render routine intravenous therapy unwarrantable. Generalized weakness, electrocardiographic changes and diarrhoea occurred in about half the patients. Signs and symptoms of toxicity in some cases made their appearance after the first dose of emetine, but in most they were not manifest until the 10th day of treatment. In a surprisingly high proportion of cases the signs were transient, in spite of continued drug administration; their severity was usually mild or moderate, with little tendency to increase, and they rarely continued moré than a week after cessation of treatment.

Indications for stopping the drug were praecordial pain (in three patients), persistent electrocardiographic changes (in two), neuritis (in one), fainting (in one), nausea and vomiting (in one), and "quivering of the muscles and weakness" (in one patient).

Emetine "neuritis" was studied, and, in common with similar cases reported in the literature it seemed attributable primarily to a disorder of the muscles rather than to a disturbance of the nervous system. The usual signs of a neuritis, such as loss of reflexes, changes in sensation, and muscular atrophy are usually absent in emetine "neuritis", and the condition, it is suggested, is a toxic myositis rather than a neuritis.

[This paper should be consulted in the original by those interested.]

A. R. D. Adams

LAMY, L. & CHEVRIER, A. M., Mlle. Action comparée de l'α (*p.* aminobenzènesulfamido) pyridine sur deux amibes parasites. [**The Comparative Action of Soludagenan on Two Parasitic Amoebae.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 149–53.

In 1942 the authors began to study the action of the sulphonamide drugs on amoebae *in vivo* and in cultures. Observations on cultures of *Entamoeba histolytica* and *E. invadens*, a parasite of reptiles, show that the former will

withstand a concentration of 1/1,000 Soludagenan [α (*p*-aminobenzenesulphamido) pyridine] but that the latter behaves in a different manner. The following observations were made in the case of *E. invadens* :—

(1) With concentrations of 1/100 to 1/500 there was no growth in the tubes.

(2) In concentrations of 1/600 to 1/2,000, cysts formed from the inoculum, but no trophozoites. Subcultures were negative.

(3) In concentrations of 1/2,500 to 1/8,000 some trophozoites and fairly numerous cysts were present after 5 days, but the vegetative forms were not seen after the 10th day, cysts only being present by then. Subcultures were negative.

(4) In a concentration of 1/10,000 there were numerous trophozoites and cysts after both 5 and 10 days, but subcultures into a medium containing 1/10,000 of the drug were negative.

(5) Below this concentration, both cultures and subcultures were unaffected.

Soludagenan therefore exerts a specific action on *E. invadens*, and is the first sulphonamide shown to be an amoebicide. The authors think it probable that other sulphonamides may be found to exert a specific action on *E. histolytica*, in which case their value in treatment would be enhanced as they also act on the accompanying bacterial infection. *A. R. D. Adams*

El Ghaffar, Y. A. **Atebrine in Amoebic Dysentery.** *J. Roy. Egyptian Med. Ass.* 1948, May, v. 31, No. 5, 456–60.

Twenty patients harbouring vegetative *Entamoeba histolytica* in the stools were treated with atebrin (mepacrine) in varying dosage. Symptoms lessened in a few days and had usually vanished in a week. No parasites (48-hour stool examinations) were seen during, or for 2 weeks after, treatment, except in one case where a few cysts were found. Concurrent infections with *Giardia intestinalis* and *Trichomonas hominis* disappeared with the larger doses of the drug ; *Ascaris* ova did not do so. *A. R. D. Adams*

Durieux, C. ; Trenous, J. ; Tanguy, F. ; Robin, C. ; Raoult, A. Recherches sur les propriétés thérapeutiques de la conessine. I. Essais préliminaires dans le traitement du paludisme et de l'amibiase intestinale. L'émétine sera-t-elle détrônée par la conessine [Durieux, Trenous & Tanguy]. *Méd. Trop.* Marseilles. 1948, Jan.-Feb., v. 8, No. 1, 7–11. II. Nouveaux essais de traitement de la dysenterie amibienne par le chlorhydrate de conessine [Tanguy, Robin & Raoult]. [**Studies on the Use of Conessine in the Treatment of Malaria and Amoebic Dysentery.**] *Ibid.* 12–31, 2 coloured graphs.

I. In 1935 a study was instituted into the African pharmacopoeia, and of the plants used locally in French West Africa for therapeutic purposes. Among these were specimens of a root, known as "*séoulou*" and identified as that of *Holarrhena africana*, which is employed for its diuretic and anti-blennorhagic properties. Analysis showed its composition to be identical with that of Kurchi, *H. antidysenterica*, long used in India as an antidysenteric ; the active principle of this is conessine, which constitutes about 60 per cent. of the total alkaloidal content. *Séoulou* appears to be identical with the "*kumbanzo*" of Mozambique, which was referred to as a febrifuge by Livingstone in 1856. During the quinine shortage in French W. Africa during 1940, the alkaloids of *H. africana* were extracted for investigation of their antimalarial properties. Iodobismuthates of the total alkaloids were not tolerated by the oral route, but on intramuscular

injection in doses of 0·2 gm. daily into 7 persons suffering from primary benign tertian malaria they were not found to control their infections.

After a study of the literature on Kurchi, a dozen cases of acute or of chronic intestinal amoebiasis were treated during 1941–2 with the hydrochloride of conessine; the salts of the secondary alkaloids, having been found to cause intolerance when given by the mouth, were eventually discarded. The results of oral and of subcutaneous injection having been found similar, the drug was usually given in cachets by the mouth in doses up to 0·3 to 0·4 gm. daily to a total of 2·4 gm. over a period of 6 to 8 days. In every case so treated the clinical symptoms rapidly subsided and the stools became normal. One patient relapsed 2 weeks after 0·75 gm. of conessine hydrochloride subcutaneously and 1 gm. of the total alkaloids by mouth; retreatment with 0·2 gm. conessine hydrochloride daily for 8 days resulted in [clinical] cure. Another case of chronic amoebiasis, previously unsuccessfully treated with emetine, acetylarsan, and other drugs, was clinically cured within a week by doses of 0·1 gm. thrice daily. In a third case of double infection with amoebae and with trichomonads, both parasites disappeared after a similar course of treatment. Conditions at the time prevented adequate follow-up of the cases to determine if parasitic cure had been obtained, and the investigation had to be abandoned until 1947.

II. Between April and September 1947, 6 Europeans and 6 Africans suffering from amoebiasis were treated with conessine hydrochloride; the clinical effects, the dosage, the therapeutic action, the side effects and the excretion of the drug in these cases were studied in detail. The initial dosage advocated is at least 0·5 gm. daily by the mouth for an adult (roughly 0·01 gm. per kilo of body weight over 5 to 6 days); this is decreased during the last days of treatment and the gross dosage advocated is 5 to 5·5 gm. There was immediate relief from pain and the disappearance of tenesmus within 48 hours in the acute cases, and the physical signs disappeared, the stools becoming formed and normal in appearance in all of them. In 7 of the 12 cases treated parasites completely disappeared; in the others, amoebae and cysts persisted. *Trichomonas* infestations were cured in a few days. Salivation occurred in two of the European patients. Insomnia appeared early and increased in intensity during treatment; it was associated with disturbing dreams, and in some cases with disorientation of time and space. Most patients developed fine tremors, which became marked and persisted for some days after the completion of treatment. Vertigo and tinnitus occurred in about half the cases.

Conessine caused none of the changes in the urine associated with irritation of, or damage to, the renal epithelium. It produced a slight but inconstant diuresis. The urinary excretion of the drug is slow; its diuretic action and its excretion through the kidneys are depicted in two graphs.

Conessine compares favourably with emetine in the control of acute amoebic dysentery, and can be safely given if the nervous and psychic manifestations attending its use are controlled by the use of one of the barbiturates.

A. R. D. Adams

Darío Fábrega, R. Una critica a la cura de amibiasis intestinal. [**A Study of the Therapeutics of Intestinal Amoebiasis.**] *Archivos Hospital Santo Tomas.* 1947, July–Dec., v. 2, Nos. 3/4, 369–82. [30 refs.] English summary. A review of the literature and discussion.

Wadsworth, G. R. **The Dysenteries.** *Med. J. Malaya.* 1947, Mar., v. 1, No. 3, 157–65, 1 fig.

A general discussion and review.

RODHAIN, J. & VAN HOOP, M. T. *Entamoeba knowlesi* n. sp., parasite de deux tortues : *Terrapina cinosternoïdes* et *Platysternum megacephalum*. [*Entamoeba knowlesi*, **n. sp. as a Parasite of Two Tortoises.**] *Ann Parasit. Humaine et Comparée.* 1947, v. 22, Nos. 3/4, 129–37, 1 fig. [12 refs.]

BROWN, E. H. **Giardia Lamblia. The Incidence and Results of Infestation of Children in Residential Nurseries.** *Arch. Dis. in Childhood.* 1948, June, v. 23, No. 114, 119–28.

The nursery in which this investigation was carried out is one of the largest and most modern in London. The incidence of *Giardia* infestation on admission in children from one to three years was 26·6 per cent. and there was no significant difference in the incidence between the age groups.

Direct examination of the stools for *Giardia* cysts is unreliable, and unless repeated examinations are made, a large number will be missed. The ether concentration method consists of the emulsification of a portion of faeces the size of a large pea in normal saline in 1 oz. screw-cap bottle ; a layer of ether is added and the bottle is then shaken. The lower layer of saline containing cysts and ova is pipetted into a centrifuge tube and spun at 1,500/min. for 5–7 minutes. The supernatant fluid is discarded and a loopful of the deposit is placed on a slide with Gram's iodine.

In a group of 86, the incidence in thirty who had previously attended a day or residential nursery was 50 per cent., but that in 56 who had not done so was only 14·3 per cent.

The great majority of the long-stay children over one year old were infested ; in one random group the incidence reached 79 per cent., but under the age of one year the incidence was low. There was a rapid rate of infestation after admission. On the other hand the incidence in adults was 3·7 per cent. on one examination. There was no significant difference in height and weight between children who had *Giardia* cysts in the stools and those who had not. On admission there was no significant difference between the stools of a *Giardia*-infested child and those of a child not infested.

The inference is that some factors other than *Giardia* must play a part in accounting for the difference between children on admission and those long resident, but no significant difference was found in the haemoglobin levels. There was no evidence of any marked inability on the part of the *Giardia*-infested children to absorb fats.

The group of *Giardia*-infested children treated with mepacrine showed a significantly greater rate of weight gain than the control group and there was a marked decrease in the incidence of loose stools.

The improvement following mepacrine was a gradual process which might be expected to occur in a chronically inflamed intestine, but there appeared to be no definite relationship between the occurrence of *Giardia* infestation and the onset of loose stools. Dietetic upsets, infections of the upper respiratory tract and psychological disturbances are probably the important factors predisposing to the onset of diarrhoea.

The conclusion is that there is no evidence to support the view that severe cases of non-specific enteritis can be attributed to *Giardia intestinalis*. The suddenness of such outbreaks and the rapidity of spread suggests some bacterial or virus cause. [See also this *Bulletin*, 1943, v. 40, 54, 699.]

P. Manson-Bahr

MOHAPATRA, G. S. **Giardiasis in Children.** *Indian Med. Gaz.* 1948, Jan., v. 83, No. 1, 14–17.

The report is based on 10 cases each of which is described separately. All the patients were children, of whom nine were under the age of 5 years.

Common symptoms were diarrhoea, prostration—in proportion to the duration of the infection, although the children usually looked well—flatulence, and poor appetite. The tongue was usually clean. Anaemia, in some degree, was always noted [no records of blood examinations are given in the case notes, so this was presumably a clinical observation]. There were frequent remissions of symptoms, usually coincident with some form of therapy.

The stools varied in colour and consistency, but at some time in each case white fatty stools were passed; in some cases this followed a period of bloody mucoid stools. Motile *Giardia intestinalis* were found in large numbers in each case; it was noted that in periods of remission the motility of the flagellates decreased.

Treatment by mepacrine [the author states "atebrin or mepacrine"], a quarter of a tablet 3 times a day for five days, effected a clinical cure in every case; in two there was a temporary relapse which necessitated a second course. However, in all cases the infection persisted for periods up to two months, although the flagellates were reduced in motility. *L. E. Napier*

LIEBOW, A. A., MILLIKEN, N. T. & HANNUM, Clair A. **Isospora Infections in Man.** *Amer. J. Trop. Med.* 1948, Mar., v. 28, No. 2, 261–73, 2 pls. [44 refs.]

In 1935, MAGATH [this *Bulletin*, 1935, v. 32, 660] summarized all information on this subject and since that time only one extensive clinical and parasitological study has appeared; this was a survey of German troops evacuated from North Africa by HERRLICH and LIEBMANN [*ibid.*, 1944, v. 41, 782].

More than half the previously recorded instances had come from countries bordering the Mediterranean. Additional infections in man have been reported from China, N. and S. Africa, the Philippines, Argentina, Brazil, Russia, Palestine, Japan, Okinawa, Venezuela, Cuba and Mexico and other areas. The present paper deals with patients evacuated from the campaigns in the Pacific. One was apparently infected in the Solomons. Five other soldiers were sent to Saipan from Okinawa.

It is possible that intra-epithelial forms were seen by KJELLBERG and described by VIRCHOW as early as 1860. It should be expected that *Isospora* would have an intracellular schizogonous cycle in analogy with other coccidia, but since the instance recorded above, only the oöcysts and their subsequent transformations leading to the development of four sporozoites in each of two sporocysts are known. GOTO has published evidence suggesting the existence of coccidiosis of the nasopharynx. The oöcysts in all the present author's patients displayed the typical features of the genus *Isospora*. The length of the freshly passed oöcyst at the commencement of segmentation is 31·1μ with a width of 11·9μ.

Development takes place *in vitro*, even when the cysts are kept in hypertonic solutions such as 2 per cent. potassium bichromate or saturated zinc sulphate.

Under conditions of room temperature on Saipan there is rapid segmentation of the sporoblast. The incidence of infection amongst soldiers evacuated from Okinawa was at least 0·75 per cent. and is similar to that of Herrlich and Liebmann's series.

Only one of the five was omitted with actual diarrhoea, but there had been a past history in three.

All but one had an eosinophilia of 14 per cent. or higher, but ova of hookworm were also present in four; and there is no evidence that this rise of eosinophilia is due to the *Isospora*.

It is probable that signs and symptoms ascribed to infection with this organism are the result of coexistent infection with other organisms. It is

particularly difficult to assess the effect of therapeutic agents since the organisms tend to diminish and ultimately to disappear. There is no dramatic response to mepacrine, quinine, tetrachlorethylene or carbarsone.

An attempt was made to discover where the organisms may occur in the gastrointestinal tract. Miller-Abbott tubes were passed in all five patients and a sigmoidoscopic examination was made in each. Samples of intestinal contents were removed from the duodenum between 8 and 10 inches beyond the ligament of Treitz and at four other levels. Oöcysts were found in the aspirated material in two patients. *P. Manson-Bahr*

MUKHERJEE, N. N. **Incidence of Coccidiosis in the Arakan.** *Indian Med. Gaz.* 1947, Dec., v. 82, No. 12, 735–6. [12 refs.]

Since the discovery of *Isospora hominis*, some 200 cases of infection by it have been reported, the highest figure in one zone being 32 from the Eastern Mediterranean. The author refers to previous records of cases in East Asia between 1920 and 1936, which varied between one and five in each locality quoted.

In the Arakan, on the Eastern frontier of South Bengal, the present author saw 14 cases of coccidiosis in about 7 months out of some 6,000 stool examinations from over 1,000 soldiers, British and Indian. Twelve of the 14 were detected by direct examination and the other two by Sheather's concentration method (sugar flotation). The findings are summarized in a table. Charcot-Leyden crystals were present in all but two cases. Most of the patients had loose, light-coloured stools with undigested food material. All cases occurred among British troops between May and October, the peak of incidence corresponding with the peak of the monsoon. Nearly all cases originated in the same area, suggesting some endemicity.

The condition was usually mild, and manifested by diarrhoea and some abdominal discomfort ; but acute dysentery and prolonged illness of 3 to 5 weeks duration occurred in a few cases. Eight of the patients harboured some associated pathogenic intestinal parasites, such as nematodes or *Trichomonas hominis*. *H. J. O'D. Burke-Gaffney*

RENS, M. R. **Balantidium coli.** *Nederl. Tijdschr. v. Geneesk.* 1948, July 24, v. 92 (iii), No. 30, 2225–8, 2 figs. on pl.

The English summary appended to the paper is as follows :—

" Description of a case of very tenacious and frequent diarrhoea caused by balantidium coli, a ciliate occurring in the intestine of man, pigs and monkeys. Our case concerned a pork butcher, who, owing to gross uncleanness, very likely had infected himself with pigs balantidia. Morphology, morbidity, occurrence, reproduction and therapy of balantidium are further gone into.

" Whereas the very numerous medicaments mentioned in the literature were not or only slightly successful in treating the disease, a speedy and complete recovery was brought about in the case described above by a 10 days' cure of 750 mg. enterovioform ' Ciba '."

RELAPSING FEVER AND OTHER SPIROCHAETOSES

COLLIER, W. A. Die Verbreitung der Leptospiren in Niederländisch-Indien. [**The Distribution of Leptospirae in the Dutch East Indies.**] *Acta Tropica.* Basle. 1948, v. 5, No. 2, 135–59.

Eighteen sorts of leptospirae have been isolated in the Dutch East Indies, and serological evidence has been found of the presence of 3 others. Of special

interest is *Leptospira bataviae* which was thought to have a very circumscribed distribution until it was reported from N. Italy [see MINO, *Bulletin of Hygiene*, 1940, v. 15, 369].

The nomenclature of these leptospirae presents difficulties. On the one hand, the same organism has been given different specific names by different authors, while, on the other, certain workers believe that separation into species is not justifiable. Furthermore such words as "type" and "group" are used with a significance different from the meaning accepted in systematics. Collier holds that the antigenic structure of leptospirae is constant, and that serological reactions should be used as the basis of classification. The species to which any strain belongs can be determined by agglutination-lysis tests. A species may, however, contain "races" which can be separated only by absorption tests. These have been called "biotypes" in the case of *L. icterohaemorrhagiae* [GISPEN & SCHÜFFNER, *Zent. f. Bakt.* I. Abt. Orig., 1939, v. 144, 427] but Collier suggests that they should rank as Subspecies or Races—preferably the former. A list is given of the 24 species recognized by the author as being present in South-East Asia. Details are set out of each type strain—host, place of isolation, and original description; then follow any synonyms, and the distribution of the species in South-East Asia. [The information cannot be summarized.] Subspecies are noted for *L. autumnalis* (*L. autumnalis autumnalis* and *L. a. rachmati*); *L. bataviae* (*L. bataviae bataviae* and *L. b. letalis*); *L. icterohaemorrhagiae* (*L. icterohaemorrhagiae icterohaemorrhagiae* and *L. i. incompleta*). One table shows the areas in South-East Asia where human infections with the different species have occurred; another deals with surveys of different animals, and records the numbers tested and the species of leptospirae found in the different places. *J. C. Broom*

YAWS

GOODMAN, L. **Sudden Death after Intravenous Sodium Bismuth Tartrate.** *Brit. Med. J.* 1948, May 22, 978–9.

Previous reports indicate the toxicity of bismuth salts given intravenously, and their action on the central nervous system and heart in animals. Despite the very extensive use of bismuth preparations in the treatment of yaws, few fatalities have been reported.

Three African women were inadvertently given, intravenously, 10 grains (650 mgm.) of sodium bismuth tartrate (Sobita) in aqueous solution. Two who had received 13 and 10 mgm. of Sobita per kgm. body weight collapsed and were dead in 2 minutes. Post mortem examination showed that the only notable abnormality was an unusual flabbiness of the heart. The cause of death was not recognized until the presence of bismuth in the liver was reported. None of the women had convulsions.

The third woman had received 11 mgm. of Sobita per kgm. body weight and collapsed 6 minutes later. She was given nikethamide (1 ml.) and artificial respiration was applied. She recovered consciousness and was given "Ametox" and intravenous salines [amounts not stated] but a blue line on the gums appeared on the third day. Oliguria started early and resulted in anuria by the fifth day. After intravenous administration of sodium sulphate solution [no details of dosage are given] urinary excretion commenced and increased until on the 10th day when death occurred, 16 oz. (450 ml.) were passed. All urine passed after the administration of the Sobita contained albumin, red blood corpuscles and casts. Blood urea nitrogen was over 200 mgm. per 100 ml. on the last three days of life. Post mortem findings included

a marked blue gingivitis, a litre of clear, pale amber, peritoneal fluid, a soft enlarged liver with recent fibrinous adhesions to adjacent viscera and an inflamed lower colon and rectum with small petechiae. The kidneys were very pale and swollen, with complete destruction of the tubular epithelium and many granular and fatty casts. Kidneys and liver contained much extremely finely divided fat, otherwise the liver tissue showed little change. The relative quantities of bismuth per kgm. liver tissue in the three cases were 40, 30 and 23 mgm. respectively.

[How three, apparently consecutive, patients were inadvertently given intravenously doses of Sobita of three times the maximum intramuscular dose is not reported. No reference is made to any previous bismuth treatment these women may have received.] *C. J. Hackett*

Downing, J. G. **Yaws in Massachusetts.** *New England J. of Med.* 1948, July 1, v. 239, No. 1, 17–18, 2 figs.

Two cases in Negroes who had lived in Jamaica.

LEPROSY

Martinez Dominguez, V. A proposito de la clasificación de la lepra. [**Proposals for the Classification of Leprosy.**] *Med. Colonial.* Madrid. 1948, July 1, v. 12, No. 1, 21–49, 10 figs.

A discussion on existing and proposed classifications.

Schujman, S. Tratamiento chaulmoógrico intensivo (intramuscular e intradérmico) en los casos lepromatosos no beneficiados con las dosis bajas de la misma medicación. Primeros resultados observados. [**Treatment of Lepromatous Forms of Leprosy with Large Doses of Chaulmoogra.**] *Prensa Méd. Argentina.* 1948, Mar. 19, v. 35, No. 12, 501–5, 3 figs.

The author, believing that the poor results of the treatment of leprosy were due to the smallness of the doses generally given, selected 30 patients suffering from the lepromatous form who had been under treatment for many years, some up to 10, on the usual doses of 30–50 cc. a month. Of these only five had shown any improvement, 10 had remained stationary and 15 were worse. He started giving them larger doses of 90–150 cc. a month. On the whole these doses were well tolerated, the local pain soon passed off and after eight months of this treatment none was worse, one only had remained stationary, 29 had improved, six of them "greatly improved". Photographs show the condition before starting the intensive course and at the end of it; the changes depicted are very marked. *H. Harold Scott*

Fernandez, J. M. M. & Bergel, M. Recentes investigações sôbre o emprêgo metanal-sulfoxilato de sódio no tratamento de lepra. [**Formaldehyde-sulphoxylate of Sodium in the Treatment of Leprosy.**] *Hospital.* Rio de Janeiro. 1948, Apr., v. 33, No. 4, 549–52. [11 refs.]

The authors argued thus for trying this drug: Soule and McKinley have shown that an atmosphere rich in oxygen affects cultures of [what they thought to be] *Myco. leprae* [see this *Bulletin*, 1933, v. 30, 238]; Grau Triana has shown the effect exerted by oxidases on such cultures [*ibid.* 1945, v. 42, 212]. The action of reducing agents on lower, unicellular organisms is different from that on the higher organisms, and therefore it may be possible to disturb [even destroy] the vital function of a pathogenic agent without injuring the body infected by the use of such agents.

Sodium formaldehyde sulphoxylate ($NaHSO_2.CH_2O.2H_2O$) is a compound of sodium hydrosulphite ($Na_2S_2O_4$) and formaldehyde. The authors prepared a 10 per cent. solution of this drug in doubly distilled water and injected daily 6 gm. [so stated] of it in two doses, intravenously and intramuscularly, so as to keep the organism under continuous action of the drug. It was given thus for 10–15 days and renewed after an interval of 5–7 days. Given orally, it was badly absorbed and caused diarrhoea. They treated 12 advanced lepromatous patients in this way and report favourably upon the drug—softening and diminution of the lepromata, diminution in numbers and staining properties of the bacteria. Later, to assist the reducing action they gave ascorbic acid also, but the results were no better, in fact some seemed to recede. It is thought that, in spite of the reducing action, the ascorbic acid may in some way interfere with that of the metanal and sulphoxylate.

Three hypotheses are put forward regarding the beneficial action of the drug: (1) That it is not specific, but is merely a reducing agent. (2) That it acts as a specific poison in a certain stage of " oxide reduction " of the *Myco. leprae*. (3) That it acts as a poison on [presumably interferes with] some essential metabolism required by the organism. The authors hope to carry out more tests on a larger scale. *H. Harold Scott*

Scholten, C. Tierexperimentelle Studien zur Chemotherapie der Lepra. [**Animal Experimental Studies on the Chemotherapy of Leprosy.**] *Ztschr. f. Hyg. u. Infektionskr.* 1944, Nov. 12, v. 126, Nos. 1/2, 1–6.

HELMINTHIASIS

Gaud, J. & Maurice, A. Foyers de bilharziose vésicale dans le Sous. [**Foci of Urinary Schistosomiasis in the Sous Region.**] *Bull. Inst. Hyg. Maroc.* 1946, v. 6, 61–2.

The existence of urinary schistosomiasis in the Wady Sous region of Morocco is confirmed. In three foci (Km. 44, Aït Baha and Tanalt) the infestation rates in children in July 1947 were respectively 10, 79 and 86 per cent. The incidence seemed to be greater in the mountain (Anti-Atlas) than in the plain. Malacological investigations were negative. *H. J. O'D. Burke-Gaffney*

Cram, Eloise B. [**Studies on Schistosomiasis.**] **Objectives of Research, Sources of Material, and General Methods.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 49–54.

The maintenance of a steady supply of material for schistosomiasis research in the United States was an essential part of a project designed primarily for the needs of the military forces and secondarily for the longer-range concern of public health. The principal sources of material are stated. Supplies of eggs of *S. mansoni* were furnished for over 3½ years from a rhesus monkey which had been experimentally infected. Eggs of *S. haematobium* were obtained from a hamster, experimentally infected, and from a fat-tailed gerbil, *Pachyuromys duprasi*, also experimentally infected. Eggs of *S. japonicum* were supplied by six Philippine dogs. Snail intermediaries were shipped from various sources either as adults or eggs.

The methods of shipment of snails, eggs, their subsequent treatment and the general methods employed in the laboratory for collecting schistosome eggs and exposing snails to infection, are described. *J. J. C. Buckley*

WRIGHT, W. H. **The Geographical Distribution and Molluscan Intermediate Hosts of the Schistosomes maturing in Man.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 1–48. [204 refs.]

In this compilation "the schistosomes maturing in man" are restricted to the three well-known species *S. haematobium*, *S. mansoni* and *S. japonicum*, and the author reviews concisely the current position with regard to the validity and status of other less well-known or controversial species reported from human hosts. Doubtful or questionable distribution records of the three main species are discussed and considerable efforts have been made to produce a complete and authentic list of localities.

The names of molluscan intermediaries are listed with the localities, together with annotations relating to their nomenclature, and status as authentic or merely inferential hosts. The list of 201 references is classified under geographical headings. *J. J. C. Buckley*

BERRY, E. G. **Snails collected for the Schistosomiasis Investigations.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 55–69, 1 fig. on pl.

Collections of snails for schistosomiasis research in the United States were made by the author from 11 States: Michigan, Kentucky, North Carolina, South Carolina, Georgia, Florida, Mississippi, Louisiana, Texas, Utah and California. Particular attention was given to the collection of members of the family Amnicolidae, of which the genus *Oncomelania* is a member.

From more than 150 localities in these States, 54 species of Amnicolidae, Pomatiopsidae and Planorbidae (including the genus *Tropicorbis*) were taken. The species in this collection are listed together with those of another collection. In all, 103 species and sub-species were identified, representing nine families of molluscs. *J. J. C. Buckley*

CRAM, Eloise B., FILES, Virginia S. & JONES, Myrna F. **Experimental Molluscan Infection with *Schistosoma mansoni* and *Schistosoma haematobium*.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 81–94. [25 refs.]

The authors exposed 23 species and subspecies of native American snails of the family Planorbidae and 4 species of non-planorbids to infection with the Puerto Rican strain of *Schistosoma mansoni*. The only susceptible species was found to be *Tropicorbis havanensis* (Pfeiffer), which produced cercariae infective to mice. Exposure of American snails to infection with *S. haematobium* gave negative results; but the authors comment upon their lack of success in infecting *Bulinus contortus* and *Physopsis africana* with *S. haematobium*.

J. J. C. Buckley

GELFAND, M. **Bilharzial Affection of the Ureter. A Study of 110 Consecutive Necropsies showing Vesical Bilharziasis.** *Brit. Med. J.* 1948, June 26, 1228–30. [10 refs.]

The ureter is often affected in bilharziasis. In 110 consecutive postmortem examinations in Salisbury, Southern Rhodesia, on adult Africans from a highly endemic bilharziasis area, ureteral dilatation was found in 25 cases; three others had ureteral strictures. In 16 of the 25 the dilatation was unilateral [but see below]; in 6 of these it affected the whole length of the ureter, in 5 the middle and lower thirds, and in the remaining 5 the lowest third only. In 9 of the 25 the dilatation was unilateral (*sic*), [? bilateral]; in 2 of these the whole length of the ureter was involved, in 4 the middle third, and in 3 the middle and lower thirds.

The diseased portions of the ureter are readily identifiable by changes in their Nlour, texture and appearance ; these were usually found in the lowest third. coo dilatation occurred in the absence of such changes. If the cause of the dilatation were stenosis it would be expected that the whole of the ureter above the constriction would be dilated, and the dilatation would not be confined to the site of the disease, as was found to be the case. The dilatation is therefore directly attributable to damage to the ureteral wall by the disease. The disease is thus associated with ureteral dilatation, but rarely with stenosis as has previously been thought. The dilatation and thickening of the ureteral wall lead to impaired peristalsis with stasis, and possibly reflux of urine from the bladder. These in turn cause hydronephrosis.

Eight cases of hydronephrosis were encountered, and 4 of these, in which the condition was bilateral, showed ureteral dilatation. One case of these four was attributable to a congenital abnormality of the ureteric openings in the bladder. In one case of ureteral stenosis, there was hydronephrosis on the same side as the stricture ; in 2 of the 3 cases with ureteral stenosis there was no hydronephrosis. Three cases of carcinoma of the bladder were associated with bilateral hydronephrosis, due to lower ureteral obstruction by the growths.

Histological section of the bilharzial disease in the ureters showed ova to be present in the submucosa and between the muscle bundles in the muscular layer. Tubercle formation, so common in the appendix, was not seen. The separation of the muscle fibres results in their atrophy, and the affected portion of ureter becomes dilated, elongated and tortuous. The changes in the ureteric orifices in the bladder were inconstant, but in no case was there true stenosis with occlusion. *A. R. D. Adams*

Ibrahim, M., Sorour, A. & El-Sherif, A. **The Role of Urinary Bilharziasis in the Production of Hypertension and Cardiac Decompensation.** *J. Roy. Egyptian Med. Ass.* 1948, May, v. 31, No. 5, 444–62. [10 refs.]

The authors review their findings in 89 cases of hypertension (57 " essential " and 32 " nephritic "). Four (7 per cent.) of the cases of essential hypertension had associated urinary bilharziasis ; 13 (40·6 per cent.) of those with renal hypertension had evidence of the disease ; 6 (18·7 per cent.) other cases were considered probably to be of bilharzial origin. Secondary infection of the kidneys following a urinary bilharzial infection leads to renal hypertension ; if this is due to a one-sided lesion nephrectomy may be considered.

A. R. D. Adams

Cram, Eloise B. & Files, Virginia S. **Experimental Mammalian Infection with the Schistosomes of Man. I. Laboratory Animals as Source of Supply of Adult Schistosomes and their Ova.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 101–5.

Attempts to establish and maintain the three species of schistosomes of man in laboratory animals were successful in the case of *S. mansoni* and *S. japonicum* but not with *S. haematobium*. Monkeys were infected with cercariae of *S. mansoni* from *Australorbis glabratus* by various methods, which are described, but their relative effectiveness could not be determined. Subcutaneous injection of *S. mansoni* cercariae into a dog gave negative results. From various trials with smaller laboratory animals it was concluded that the best results derived from intraperitoneal injections of mice and hamsters. Dogs were found to be excellent hosts for *S. japonicum* and golden hamsters and white mice were also favourable hosts, though in heavy infections of the latter animals, the mortality was high in the prepatent period. *J. J. C. Buckley*

CRAM, Eloise B. & FIGGAT, W. B. **Experimental Mammalian Infection with the Schistosomes of Man. II. Comparative Study of *Schistosoma mansoni* and *Schistosoma japonicum* Infections produced by Immersion and by Intraperitoneal Injection.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 106–8.

Hamsters were exposed to infections either by immersion or by injection with known numbers of cercariae, in two experiments in which *S. mansoni* and *S. japonicum* were used respectively. With *S. japonicum*, 49 per cent. of the cercariae developed as the result of the immersion method and 51 per cent. by the injection method. With *S. mansoni* 33 per cent. of the cercariae developed from the immersion method and 19 per cent. from the injection method.

J. J. C. Buckley

OTTOLINA, C. El problema clinico de la Schistosomiasis Mansoni ante nuevos metodos diagnosticos y sus resultados. [**New Diagnostic Methods for Schistosomiasis Mansoni.**] *Medicina.* Mexico. 1947, Dec. 25, v. 27, No. 546, 553–64. [27 refs.]

The author in dealing with this clinical problem offers a few remarks on treatment, but these contain nothing new and the main part of the paper is on the question of diagnosis. He quotes various reports showing that examination of the faeces yields but a comparatively small proportion of patients actually infested, from 2 to 9 per cent. Rectal biopsy, however, demonstrates some 20 per cent. Even when the ova are present in the rectal tissues in large numbers ("many thousands" says the author) they may not pass into the lumen and so not appear in the faeces; in short, the absence of ova in the faeces is no proof that *Schistosoma* infestation does not exist. Even a positive rectal biopsy does not *prove* active disease unless the ovum seen contains a living miracidium. Another advantage of the method is the diagnosis of latent or asymptomatic schistosomiasis and of extinct infestation. Cases, he states, may be divided into four groups: (1) *True latent infestations*, the worms being alive and the ova some living, some dead, but there are no clinical signs or symptoms. (2) *Latent extinct*; the worms have died recently and a few living ova may still be present, again without symptoms. (3) *Active disease*; live worms, live eggs and symptoms present. (4) *Extinct infestation*; worms dead and no live ova seen even after repeated examination. *H. Harold Scott*

WARD, P. A., TRAVIS, Dorothy & RUE, Ruth E. **Methods of establishing and maintaining Snails in the Laboratory.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 70–80, 2 figs.

The methods employed in maintaining in aquaria amnicolid snails known to serve as intermediaries for *S. japonicum*, are described in detail, together with observations on their breeding habits in the laboratory. *Oncomelania quadrasi* bred satisfactorily in the conditions described but the propagation of *O. nosophora* and *O. hupensis* was more limited. *J. J. C. Buckley*

WARD, P. A., TRAVIS, Dorothy & RUE, Ruth E. **Experimental Molluscan Infection with *Schistosoma japonicum*.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 95–100.

Twelve species of American snails, of the family Amnicolidae, were exposed to infection with *Schistosoma japonicum* in 1945, and five species of Amnicolidae and Pomatiopsidae in 1946. One species, *Littoridina monroensis*, proved to be particularly attractive to miracidia, but failed to develop sporocysts. Of 286

specimens of the species *Pomatiopsis lapidaria* which were exposed, 6 developed sporocysts resembling those of *S. japonicum* but this result is regarded as inconclusive. Control experiments with *Oncomelania nosophora* generally produced positive results. *J. J. C. Buckley*

JONES, Myrna F. & BRADY, F. J. **Survival of *Schistosoma japonicum* Cercariae at various Temperatures in several Types of Water.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 131–6, 1 fig.

The authors noted experimentally the following death points for cercariae of *Schistosoma japonicum* : 4 hours at 40°C., 20 minutes at 45°C., 3 minutes at 50°C., and one minute at 55°C. With cercariae of *S. mansoni* the results were : 20 minutes at 45°C., 2 minutes at 50°C., and 1 minute at 55°C.

Within the range of 5°C. to 40°C., the survival of the cercariae of *S. japonicum* decreased as follows : At 5°C., a few survived 8½, but none survived 10½ days ; at 10°C., some survived 4½, but none survived 6½ days ; at 20°C. and 25°C., some survived 2 days, but none survived 3 days ; at 30°C., the maximum survival observed was 22 hours ; at 40°C., some survived 3 hours but none survived 4 hours.

The survival of cercariae at temperatures ranging from 5°C. to 35°C., in a variety of waters, was also tested, namely : ammonia-free distilled water buffered at *p*H 7·0 to 7·1 ; a slightly alkaline raw surface water obtained from a filter plant ; a more alkaline water from a pool containing dead leaves and other plant débris ; a raw water acidified by contact with peat moss ; and water from aquaria in which stock snails, *Oncomelania quadrasi*, were living. The *p*H of the more acid water was 5·5 to 6·5 and that of the other raw waters 7·2 to 8·4. It was found that the survival of the cercariae at each temperature was the same in all the raw waters, irrespective of different *p*H values. Their survival in buffered distilled water at 20°, 25° and 30°C., was the same as in the raw waters, but was less at 5°C. and rather longer at 35°C.

J. J. C. Buckley

BOZICEVICH, J. & HOYEM, Helen M. **Intradermal and Serological Tests in Patients with Schistosomiasis Japonica.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 199–212.

" Intradermal and complement fixation tests were conducted on a group of 474 patients demonstrated to have or to have had schistosomiasis japonica. The antigens were prepared from cercariae and adults of *S. mansoni*. Intradermal tests with an antigen prepared from cercariae gave fewer falsely positive reactions with unexposed control individuals than did antigen prepared from adult worms. The use of adult worm antigen resulted in a higher percentage of positive intradermal reactions than did the cercarial antigen. The complement fixation test gave a higher percentage of positive reactions than did the intradermal test. The optical dilution of the cercarial antigen could not be determined because of insufficient material.

" The results of both the intradermal and complement fixation tests gave better correlation with results of the stool examinations conducted in the United States than they did with those conducted overseas. Early, effective therapy may be the factor which would explain the discrepancy in these results.

" Because of the conditions under which this investigation was conducted, the immunological findings proved to be less reliable than did the stool examinations in the diagnosis of the disease.

" For this reason, improvement will have to be effected in immunological methods before such tests can be reliably employed in diagnosis."

JONES, Myrna F., NEWTON, W. L., WEIBEL, S. R., WARREN, H. B., STEINLE, Mary L. & FIGGAT, W. B. **The Effects of Sewage Treatment Processes on the Ova and Miracidia of** *Schistosoma japonicum*. *Nat. Inst. Health Bull. No. 189*. Wash. 1947, 137–72, 1 fig.

The sewage treatment processes which are considered in this report in relation to their effect in destroying schistosome eggs and miracidia or in relation to their effect in concentrating eggs and miracidia in streams which might contain potential snail hosts, include the following: Primary sedimentation, anaerobic digestion of sludge, air drying of sludge, the activated sludge process, filtration with a trickler filter, and intermittent sand filtration. After a discussion of sewage and sewage treatment generally, with special emphasis on the processes concerned in the investigation, the technique and procedures employed in testing their effect on eggs of *S. japonicum* are described in detail.

Primary Sedimentation.—From tests carried out in a 19-inch column of sewage it was found that quiescent sedimentation for 5 minutes removed 25 per cent. of the eggs; 10 minutes, 47 per cent.; 30 minutes, 80 per cent.; 1 hour, 97 per cent., and two hours, 98 per cent. The settling rate was estimated as varying between 0·33 and 1·4 inches per minute. Although some eggs could escape with the effluent in primary tanks, it is concluded that the majority would be removed by primary sedimentation during the normal detention period.

It was found that raw and institutional sewage would not permit hatching in 24 hours but did not destroy the eggs in this time. In a dilution of one part of raw sewage to three parts of water, or one part of settled sewage to two of water the eggs would hatch.

Anaerobic sludge digestion.—Experiments were set up to determine how long the eggs could survive in the sludge digestion sections during this process. At 75° to 85°F. during the first week, about ¼ of the eggs were rendered incapable of hatching. This reduction continued during the second week and was greatest in the third week and there was no hatching on the 24th day of digestion. It is believed, however, that the temperature and time factors played a large part in this reduction in the viability of the eggs.

Sludge drying.—In drying digested sludge many eggs were mixed and allowed to dry for varying periods. It was found that the retention time on the drying bed was more closely related to destruction of the eggs than was the moisture content, so long as the latter was 40 per cent. or over. Thus, sludge which is to be dried to 60 or 70 per cent. moisture content before disposal would need to be retained for 3 weeks to ensure the destruction of any eggs which might be present.

Trickling filter treatment.—This secondary treatment of the effluent from primary sedimentation tanks which sometimes may carry over with it schistosome eggs, was tested in relation to its effect on the eggs. It was found that filtration reduced the number of eggs but in all experiments some got through. Secondary settling of the effluent reduced these but failed to remove them entirely. In such conditions additional treatment such as chlorination is indicated.

Activated sludge.—Experiments were set up to determine the survival of schistosome eggs in activated sludge. Hatching of most of the eggs occurred in the first 24 hours and very few miracidia were recovered after 3 days, indicating that the activated sludge is an excellent hatching medium. A post-treatment process designed to destroy or remove miracidia is again indicated.

Intermittent sand filtration.—In five experiments, employing this process, in which the rate was 100,000 gallons per acre, per day, sand with an effective size of 0·3 mm. and a uniformity coefficient of 2·6 being used, it was demonstrated to be an efficient method of removing eggs of *S. japonicum* from sewage

No eggs nor miracidia were ever recovered from the filter effluent, nor did samples of sand from lateral borings at 6 to 10 inches reveal any eggs. Vertical borings showed that the majority of the eggs were held in the top 1·5 inches of sand and only a few were recovered at 2 to 3 inches from the top.

J. J. C. Buckley

JONES, Myrna F. & BRADY, F. J. **Effects of Water Treatment Processes on Schistosome Cercariae.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 109–30. [10 refs.]

Various laboratory tests were carried out with regard to the effects, on cercariae of *S. japonicum* and *S. mansoni*, of the water treatment processes (1) clarification, (2) filtration and (3) chlorination.

(1) The effect of coagulation with alum and soda ash on cercariae of *S. japonicum* was tested in a variety of concentrations and it was concluded that the addition of as much as 32 grains of ammonium alum per gallon, with appropriate amounts of soda ash, was inadequate against the cercariae. This amount of alum is in excess of that used in municipal water plants.

(2) The effect of filtration through Seitz-type filter pads was tested on cercariae of *S. mansoni*. With the use of heavy concentrations of cercariae in three experiments, none was recovered in any of the effluents.

(3) The following chlorine compounds were tested: High test calcium hypochlorite (HTH powder); chloramine solutions, formed by adding HTH powder to water containing the ammonium ion; Halazone tablets; and succinchlorimide.

The results of all these tests, in which both *S. mansoni* and *S. japonicum* cercariae were generally used, are described in detail and cannot satisfactorily be summarized. In general, the cercaricidal value of the chlorine compounds used was favourably reported upon.

In addition to chlorine compounds, two iodine-containing compounds were tested; namely, potassium permanganate/iodide/iodate-citric acid tablets and " Bursoline " tablets. The former compound, when used at the prescribed dose of one tablet per litre of water, killed cercariae in 5 minutes or less. In testing the compound " Bursoline ", particular attention was given to the type of water used in the experiment, *e.g.*, filtered river water; unfiltered river water; water to which leaf infusions had been added; water from an aquarium in which *Bulinus* snails had been kept. This compound was effective at a rate of one tablet per litre in clear water but its action diminished in water having increased organic content. It is remarked that this factor might also affect the cercaricidal value of chlorine compounds.

Miscellaneous cercaricidal tests were carried out with several other chemical agents; a germicidal rinse, Mikroklene; the surface active agents Aerosol OT, Nacconol, and Roccal; copper sulphate; and a DDT emulsion.

Mikroklene.—In a concentration of 1 gm. per litre, all cercariae were killed in 3 to 5 minutes. The presence of organic matter appeared to have little influence on its action.

Nacconol (*alkyl-aryl sodium sulphonate*).—Killed cercariae in 3 minutes in a concentration of 0·4 gm. per litre (active Nacconol) and within 10 minutes at 0·02 gm. per litre. At 0·01 gm. per litre (10 p.p.m), cercariae were killed within 25 minutes.

Roccal (*alkyl dimethyl ammonium chloride*).—In the higher concentrations, 1 : 5,000 and 1 : 10,000, cercariae were killed in 5 minutes. At 1 : 100,000 (10 p.p.m), all were dead within 30 minutes in filtered river water at 30° to 31°C. It is concluded that Roccal is an effective cercaricide, especially with alkaline waters such as *S. mansoni* cercariae would occur in naturally.

Aerosol OT (*dioctyl sodium sulphosuccinate*).—The tests showed that only in relatively concentrated solutions was this compound effective but that in non-lethal concentrations it might enhance or accelerate the effects of other cercaricides.

Copper sulphate.—Tested in concentrations of 5, 10 and 50 p.p.m, it proved effective only at 50 p.p.m, or more. It could not be relied upon at 5 or 10 p.p.m to kill cercariae within a reasonable time.

DDT in emulsion with Triton and xylene.—In limited tests this proved to be not an effective cercaricide in concentrations of 0·05 and 0·1 p.p.m, but at 10 p.p.m killed cercariae within 75 minutes. *J. J. C. Buckley*

Jones, Myrna F. & Hummel, Mirriel S. **The Effect of Chlorine and Chloramine on Schistosome Ova and Miracidia.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 173–9.

" Hatched miracidia of *S. japonicum* were killed within 30 minutes after chlorination with total 30-minute residuals of 0·2 and 0·4 p.p.m. Similarly, they were killed in chloramine solutions with 30-minute chloramine residuals of 0·3 and 0·4 p.p.m. *S. mansoni* miracidia were killed within 30 minutes after chlorination which resulted in total residuals at 30 minutes varying from 0·2 p.p.m. to 0·6 p.p.m. and less than 0·1 p.p.m. free chlorine present.

" Ova of *S. japonicum* are more resistant to chlorination than are miracidia. Ova were consistently killed within 30 minutes only in tests in which the 30-minute total residuals varied from 3·9 to 11 p.p.m.

" A few ova survived 2-hour treatment with chlorine and chloramine concentrations of 1·52 and 1·65 p.p.m. and 30-minute residuals of 0·75 and 1·1 p.p.m. respectively. No ova survived in one test after an applied chloramine concentration of 1·9 p.p.m. and a 2-hour chloramine residual of 0·5 p.p.m. Ova were killed in tests with an applied chlorine of approximately 2 p.p.m. and 2-hours residuals varying from 0·7 to 1·4 p.p.m."

Nolan, M. O., Mann, Elizabeth R. & Churchill, Helen M. **The Protective Value of Chemically Impregnated Fabrics against Penetration of Schistosome Cercariae.** *Nat. Inst. Health Bull. No. 189.* Wash. 1947, 180–98, 1 fig.

" Standard army uniform materials were used in tests to determine the relative value of chemically treated fabrics as a means of protection against the penetration of schistosome cercariae. Seventy-five chemical compounds, including combinations of chemicals and emulsions, were used to impregnate fabrics and were tested for toxicity to cercariae. The tests were conducted at intervals after repeated rinses of the treated fabrics in water. Mouse exposure tests were subsequently conducted to determine the protective value of those chemicals that in the preliminary tests were most effective against cercariae and most resistant to water rinses. More than 2,000 mice were exposed to cercariae in the testing of 18 chemical compounds and emulsions used to impregnate cotton herringbone twill fatigue uniform cloth, khaki cotton uniform twill, and khaki woolen serge cloth. Since water solubility of the impregnated compounds was an important factor, the majority of the mouse exposure tests were conducted at intervals after repeated rinses of the fabrics in water. Fabrics impregnated with emulsions of the cercaricides were also tested for resistance to mild laundering with soap.

" The most effective chemical was N,N-diethyllauramide which protected mice against penetration of *S. mansoni* cercariae through at least 144 hours of rinse and afforded considerable protection even after 180 hours of rinse. The emulsion of the compound, however, was one of the least resistant to washes

with soap. The compound in acetone solution appeared to be more resistant to soapy washes than the emulsion of the compound.

" Dibutyl phthalate was somewhat less effective but provided protection for more than 96 hours of rinse. The emulsion of the compound was more resistant to soapy washes than was N,N-diethyllauramide emulsion since it lasted through five washes.

" Tests with *S. japonicum* cercariae were less numerous than those with *S. mansoni*. However, it would appear that the two species reacted in the same manner to treated fabrics.

" A measure of protection was afforded by the untreated materials. Woolen serge cloth in particular was a good mechanical barrier."

McMullen, D. B. & Brackett, S. **Studies of Schistosome Dermatitis. X. Distribution and Epidemiology in Michigan.** *Amer. J. Hyg.* 1948, May, v. 47, No. 3, 259–70, 2 figs.

" In a survey of schistosome dermatitis in Michigan, 510 beaches on 127 lakes have been examined. Of these, 351 were found to have populations of carrier snails. On 130 beaches it was possible to demonstrate the presence of the infections in the snails collected. In others, infections undoubtedly could have been found at certain times of the year when adult snails were present.

" The distribution of *S. emarginata* has been thoroughly investigated. It is most common in the northwest part of the Lower Peninsula and in the eastern section of the Upper Peninsula, and it is the most important vector for water-itch in Michigan. In a few areas *Physa* spp. have been shown to be the cause of outbreaks and in 3 or 4 lakes *L. stagnalis* was suspected of being the source of the trouble. In all of the beaches examined the 3 snails, *S. emarginata*, *Physa* spp. and *L. stagnalis*, appear in the ratio of 21 : 2 : 1, and the ratio of the infected snails was found to be 39 : 3 : 1. These ratios indicate quite well the relative importance of the 3 snails in the water-itch problem in Michigan. Water-itch is found primarily in the northern part of the Lower Peninsula and the eastern portion of the Upper Peninsula. This coincides with the density of the *S. emarginata* populations. The sporadic cases that appear in other parts of the state apparently are caused by schistosome cercariae coming from *Physa* spp. and *L. stagnalis*."

von Bonsdorff, B. **Pernicious Anemia caused by *Diphyllobothrium latum*, in the Light of Recent Investigations.** *Blood.* 1948, Jan., v. 3, No. 1, 91–102. [29 refs.]

In Finland infestation with the fish tape worm, *Diphyllobothrium latum*, is extremely common, in certain Provinces more than 90 per cent. of the population being infested. In most carriers the worm is a relatively innocent parasite, but in some it causes a macrocytic anaemia resembling pernicious anaemia although differing in its age incidence, the absence of achlorhydria in many cases and the absence of neural involvement. That the anaemia is due to the worm seems proven by the fact that the anaemia undergoes complete remission after the worm is expelled, without any further need for anti-anaemic treatment. There seems no doubt that the worm contains a powerful toxin, and theories to explain the anaemia have included varying permeability of the intestinal wall to worm toxin, individual susceptibility of the haemopoietic organs to the toxin, or an allergic factor. Complete recovery from the anaemia after the worm has been expelled implies that there is no lack of haemopoietic principle. Experiments have shown that the gastric juices of patients with fish tape worm, contain intrinsic factor, and the anaemia may occur even though the food

contains extrinsic factor, although a relative deficiency of extrinsic factor may aggravate the disease. The clinical picture gives no reason to believe that absorption is impaired; carriers of the worm seldom suffer from intestinal disturbances and glucose tolerance tests showed no deviation from the normal. Powdered worm mixed with gastric juice, meat or hog's stomach failed to destroy the anti-anaemic action of these preparations in pernicious anaemia. It is suggested that possibly any inhibition of interaction between intrinsic and extrinsic factors can only be produced by the living worm in its natural surroundings at the place where interaction occurs. By intestinal intubation and examination of aspirated material for eggs, evidence was obtained that with anaemia the worm is found higher up in the intestine than when anaemia is absent, and it is suggested that in the higher regions, the worm interferes more with the interaction between extrinsic and intrinsic factor; the border zone lies 140 to 150 cm. from the mouth, namely about the junction of the jejunum and ileum. [See also this *Bulletin*, 1948, v. 45, 97, 198, 260.]

F. Murgatroyd

Le Gac, P. Toxicité des sels d'étain vis-à-vis des plathelminthes. [**Toxicity of Salts of Tin to Tapeworms.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 452–5.

The author presents observations on several cases of Taeniasis which were successfully treated with stannous oxide (Stannoxyl). He gave 6 to 8 tablets daily and the worms were expelled in 2 to 6 days. The author also mentions a proprietary vermifuge prepared from salts of tin and metallic tin which gave similar results. The preparation is sold under the name of "Taenifuge Ercé" (Laboratoires Rabent et Carrière). It is stated to be absolutely harmless and keeps well for long periods in the tropics. In a discussion, Montel confirmed successes with Stannoxyl, which he gave in doses of 18 tablets daily (6 morning, noon and evening). No purgative, special regime or bed rest was required.

H. J. O'D. Burke-Gaffney

Williams, A. A. **Cysticercosis Cerebri mistaken for Cerebral Syphilis. Report of a Case.** *Lancet.* 1948, July 24, 144.

Thiodet, J. Manifestation rétrograde de la réaction de Casoni. [**A Late Manifestation of the Casoni Reaction.**] *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1947, Nos. 19/20, 467–8.

Stoll, N. R. El problema de la investigación de la uncinaria. [**The Investigation of Hookworm Disease.**] *Medicina.* Mexico. 1948, May 25, v. 28, No. 556, 197–206.

A review of methods used.

Tiner, J. D. & Chin, T. H. **The Occurrence of** *Ascaris lumbricoides* **L. 1758 in the Muskrat,** *Ondatra zibethica* **L.** [Research Notes.] *J. Parasitology.* 1948, June, v. 34, No. 3, 253.

Baldwin, E. **A Study of Anthelminthic Potency in relation to Chemical Constitution.** *Brit. J. Pharmacol. & Chemotherapy.* 1948, June, v. 3, No. 2, 91–107. [30 refs.]

The author tested 200 chemical compounds for detection of anthelminthic potency. Pig *Ascaris* was the test helminth used, and it is claimed that, while

the technique used has certain limitations, it is important that experimental material of nematode origin should be the basis of methods of this kind.

The results are discussed in great technical detail and should be studied in the original : but they were at variance with those of earlier investigators in most respects, especially in respect of lactones. More than 30 types of lactones were tested by the author, but not one showed activity comparable with or even approaching that of santonin (itself a lactone). This contrast with the findings of other workers is attributed by the author to the use of different *in vitro* methods : many of the observations reported in the literature have been prejudiced, in the author's opinion, by the use of annelid material.

H. J. O'D. Burke-Gaffney

DE REYES PUGNAIRE, M. Tratamiento de la elefantiasis de los miembros inferiores. [**Treatment of Elephantiasis of the Legs.**] *Med. Colonial.* Madrid. 1948, June 1, v. 11, No. 6, 441–66, 13 figs. [75 refs.]

The author reviews the various methods of treatment of elephantiasis of the legs, referring first to medical treatment, later and in more detail to surgical measures. He mentions first antistreptococcus serum and states that he has obtained good results if there is inflammation present ; with vaccines he reports " very good " results especially in accessions of elephantoid fever. He quotes records of others such as autohaemotherapy, gentian violet, fibrolysin, iodides, sulphonamides in the fever, but makes no mention of having tried these on his own patients and notes that in most cases any benefit had been only temporary. During attacks of fever he employs at the same time sulphonamides, local warmth and an ointment of ichthyol 15 gm., Tr. iodi 15 gm., camphorated oil 30 gm., with compressing bandages.

He then passes on to describe operative treatment, in particular detail Kondoleon's operation and modifications of it. He sketches the history of operative measures and then gives a fuller account of his modification of the operation with illustrations to indicate the steps, and photographs showing the intermediate and final results. He removes the fascia and aponeurosis of the legs and the dorsum of the foot with extensive dissection. In some cases a second and even a third operation are needed, but the results as depicted are, in some cases at least, remarkably good. After the operation he dusts with sulphonamide powder, then stitches the skin, without any drainage. He quotes records from the Mayo clinic giving a mortality of 4·7 per cent., and " satisfactory results " in 62 per cent.

The author gives a table of 72 patients under his care ; the methods of treatment are stated, but not the results. Of the total, 14 were treated medically and 58 had some operation, 10 the Payr-Kondoleon Sistrunck, 20 the author's method with previous resection of the muscle fascia ; three had, in addition to this, on account of chronic ulcers, a preliminary lumbar sympathectomy, 10 had extensive removal of tissue on both the front and back of the leg. He concludes that medical treatment is of much importance as an adjuvant and as preparatory to surgical measures.

H. Harold Scott

MAZZOTTI, L. Observaciones sobre la oncocercosis en Mexico. [**Observations on Onchocerciasis in Mexico.**] *Medicina.* Mexico. 1948, June 10, v. 28, No. 557, 217–24. [18 refs.]

Onchocerciasis prevails in Mexico at heights of 400–1,200 metres above sea-level and chiefly in the States of Chiapas and Oaxaca, which are sub-tropical with a heavy rainfall. The vectors are *Simulium ochraceum*, *S. callidum* and *S. metallicum*, especially the first which breeds in small collections of water moving slowly ; the two others prefer larger collections moving rapidly.

In man the nodules are often in the head, less often in the thorax and lumbar region, and usually up to six in number, but they may be many more. In 34 patients, 325 biopsies were performed: 52 per cent. of nodules were on the face (or head), 65 on the shoulder, 52 on the forearm, 39 on the hand, 44 on the thorax, 34 on the thigh and 16 on the foot. From one patient with a thigh nodule an inguinal [? femoral] gland was extirpated and 11 microfilariae were expressed from it. The skin may become of a dark greenish colour; in fact, it is known in Mexico as "mal morado" (purple disease). Sometimes allergic attacks occur with fever and local induration so that in time the skin becomes thick and hard, "woody"; these attacks are known in Guatemala as "Coast erysipelas".

Treatment is by Hetrazan, which is 1-diethylcarbamyl-4-methyl piperazine hydrochloride, in doses of 2 mgm. per kilo body weight, once on the first day, twice on the second, and thereafter three times daily for 3 weeks or more. Some of the author's patients took it for 6½ weeks, but, as tested by biopsy, the results after the longer course "were not appreciably better than after the shorter." [See also this *Bulletin*, 1948, v. 45, 532, 533.] *H. Harold Scott*

JEFFERY, G. & OLIVER-GONZALEZ, J. **Absence of *Trichinella spiralis* in Rats in Puerto Rico.** [Research Notes.] *J. Parasitology.* 1948, June, v. 34, No. 3, 254.

Negative results were obtained with 418 specimens of 4 species.

SPRUE

SPIES, T. D., GARCIA LOPEZ, G., MILANES, F., LOPEZ TOCA, R. & CULVER, Belle. **Observations on the Hemopoietic Response of Persons with Tropical Sprue to Vitamin B_{12}.** *Southern Med. J.* 1948, June, v. 41, No. 6, 523–5.

In 1947 SHORB (*J. Biol. Chem.*, 1947, v. 169, 455) found in refined liver extracts a growth factor required for *Lactobacillus lactis* (LLD factor) which was present in an almost linear relationship to the unit potency of the extracts used in the treatment of pernicious anaemia. This is probably identical with a crystalline compound, vitamin-B_{12}, and is believed to be partly responsible for LLD growth activity observed for liver extracts (RICKES *et al.*, *Science*, 1948, Apr. 16, 396). The positive response in pernicious anaemia as the result of small amounts administered to patients compared favourably with those obtained with folic acid and 5-methyl uracil (thymine), but neither of the two latter has been found to prevent, or relieve, subacute combined degeneration of the spinal cord. It is with the effect of crystalline B_{12} in patients with tropical sprue that the present communication is concerned.

The two patients with tropical sprue who were selected conformed to the criteria which have been laid down:—

(1) There was macrocytic anaemia with a red blood cell count of 2·5 million, or less, and a colour index of over 1; (2) the bone marrow contained megaloblasts and had the typical erythroblastic arrest seen in macrocytic anaemia; (3) the diarrhoea was characterized by fatty stools; (4) glossitis and weight loss were present; and (5) the patients were otherwise untreated.

When the patients were placed on a diet devoid of meat, fish, poultry, milk and eggs, basic studies were completed and each was given a single dose of 0·008 mgm. crystalline B12 intramuscularly.

In both patients (Cubans of 62 and 67 years) on the third day the soreness had disappeared from the mouth and tongue; the appetite had returned; the volume of the stools had decreased and they were less gaseous. On the sixth day the patients volunteered the information that they felt "wonderful."

The reticulocyte rise occurred on the fifth day and rose to a peak on the eighth. *P. Manson-Bahr*

HAEMATOLOGY

WILLS, Lucy. **Pernicious Anemia, Nutritional Macrocytic Anemia, and Tropical Sprue. A Discussion.** *Blood*. 1948, Jan., v. 3, No. 1, 36–56. [83 refs.]

Anaemia is only one aspect of pernicious anaemia, nutritional macrocytic anaemia and tropical sprue, the three diseases presenting fundamental differences which tend to be overlooked because of the similar response of the conditions to treatment with liver extracts or folic acid. Pernicious anaemia is a familial disease of persons of European descent, the distribution of the disease corresponding to that of the racial groups affected, but occurring in all social classes of individuals. There are atrophic changes in the fundus and cardia of the stomach, with associated achylia gastrica, an increased plasma bilirubin, the presence of methaemalbumin in the plasma, iron in the tissues and other evidence of a haemolytic factor, and frequently subacute combined degeneration of the cord. The disease, including the neural changes, can be successfully treated with crude or purified liver extracts given parenterally or orally, with proteolysed liver extract by mouth, with different preparations of hog's stomach by mouth, and with digests of beef muscle or autolysed yeast with normal human gastric juice. Folic acid and its conjugated forms produce haematological remission, often suboptimal, and an immediate sense of well-being, but they are without benefit on the cord changes.

Nutritional macrocytic anaemia occurs mainly in tropical and subtropical areas, but the disease is associated with poverty, with a low calorific, largely or entirely vegetarian diet, with pregnancy and lactation, and with certain diseases, such as syphilis or particularly chronic malaria, which result in a hypertrophied reticulo-endothelial system. There are no significantly consistent changes in the gastric mucosa or secretion. There is no evidence of increased haemolysis except in areas with a high incidence of malaria. In the haemolytic type there are increased serum bilirubin values, a positive Schumm test, an increased urobilin output, yellow coloration of the skin and fat, splenomegaly and sometimes hepatomegaly, and histological evidence of a hyperactive reticulo-endothelial system. Both the non-haemolytic and haemolytic types of the disease respond to crude liver extracts given orally or parenterally, and to autolysed yeast extracts. Relapses do not occur after cessation of treatment if the diet is maintained at a satisfactory level; folic acid acts as in pernicious anaemia. The haemolytic type as in Macedonia is sometimes very resistant to treatment but some cases respond to enormous doses of liver extracts or Marmite.

Sprue has usually a gradual onset and is associated with residence in a warm climate, but affects Europeans rather than pure Indians or Negroes. Many of the patients have been well fed and there is little evidence for a direct nutritional origin for the altered intestinal absorption which conditions the ultimate deficiency. The disease is normally afebrile throughout, but a possible infective origin has been suggested by certain explosive and locally concentrated outbreaks which have occurred. Lesions of the central nervous

system do not occur and apart from changes in the bone marrow and general inanition with decrease in organ weight, especially of the heart and liver, there are only slight anatomical changes detectable at autopsy. The disease responds to a high protein diet with liver extract or folic acid. Blood transfusion in the critically ill and sulphaguanidine where there is excessive diarrhoea may help.

In all three conditions, the classic picture of panhaemopoietic dystrophy is present; it is characterized by a megaloblastic erythropoiesis, a similar disturbance in the myeloid series with pathological macro-myeloid cells, and reduction and abnormality of thrombocytes. The general opinion is that the changes in the cells of the marrow and blood are identical in the three diseases. The panhaemopoietic dystrophy possibly results from a breakdown of an intracellular enzyme system, but the deficiencies causing the breakdown differ. In pernicious anaemia there is a genetic fault which results in a persistent and irreversible failure in the formation or absorption of the liver factor, and possibly of a neurotrophic factor. In endemic nutritional macrocytic anaemia there is an unconditioned food deficiency, the deficiency being in a factor other than the liver principle, possibly a co-enzyme present in or associated with good biological protein and the vitamin B_2 complex; in areas of high malarial incidence a haemolytic factor may also be present. Tropical sprue is associated with a functional disorder of the intestine, possibly a failure in phosphorylation of fatty acids, glycerol and glucose, but the cause of this functional breakdown is unknown. *F. Murgatroyd*

TROWELL, H. C. **Tropical Macrocytic Anaemia and Nutritional Macrocytic Anaemia.** *South African J. Med. Sci.* 1947, Jan., v. 12, No. 1, 21–31. [57 refs.]

There appears to be no valid distinction between macrocytic anaemia associated with pregnancy and nutritional macrocytic anaemia not associated with pregnancy. Similarly, there appears to be no real distinction between the macrocytic anaemia of pregnancy in warm climates and that of temperate regions; some confusion arises because the blood and bone marrow have not always been clearly described in tropical anaemia and because many of the tropical cases are complicated by a light helminthic infection or mild relapsing malaria. In the present paper, the author analyses 63 cases of anaemia, of which 6 were associated with pregnancy, in Uganda. The aetiology of the anaemia in most of the cases was multiple, 80 per cent. of the patients harbouring hookworms and 31 per cent. showing malaria parasites. Most patients had a dual deficiency of iron and liver principle, giving rise to a dimorphic anaemia. Such an anaemia can often be determined from the appearance of a carefully spread thin blood film. With a dual deficiency, the film presents neither the picture of hypochromic cells with little anisocytosis such as is seen with pure iron deficiency, nor that of evenly stained flattened cells with much anisocytosis such as is characteristic of a pure deficiency of liver principle. In films of dimorphic anaemia, the central fields show solid-looking cells, perforated with one or more vacuoles, interspersed with a few densely stained thickened cells, and moderate increase of anisocytosis, while the peripheral fields show a few thickened cells and many flat cells, which are evenly stained, and there is increased anisocytosis. It might be expected that macrocytic orthochromic anaemia should, like pernicious anaemia, react to liver but not to iron; but out of 24 cases tested with crude liver extracts, 5 showed no response and 19 responded, whereas out of 14 cases tested with iron, 6 responded very well, 4 responded fairly well and 4 showed no response. In like manner, neither normocytic nor even microcytic anaemia appeared to be due always

to a single deficiency; even microcytic anaemia responded to crude liver extracts. Although liver extracts were more effective than refined, neither was as effective as in pernicious anaemia, and it is, therefore, considered that the deficiency present in the tropical anaemia is not identical with that of pernicious anaemia. Further, nutritional macrocytic anaemia as seen in Uganda can be distinguished from pernicious anaemia in the stained film, the bone marrow is not megaloblastic in the strict sense of the term, and indeed the anaemia is often not macrocytic; it may be normocytic or microcytic and it is usually associated with some degree of iron deficiency and a varying parasitic infection. *F. Murgatroyd*

Watson, Janet, with the technical assistance of Albert W. Stahman & F. P. Bilello. **The Significance of the Paucity of Sickle Cells in Newborn Negro Infants.** *Amer. J. Med. Sci.* 1948, Apr., v. 215, No. 4, 419–23. [46 refs.]

The rarity of sickle cell disease in infancy is surprising in view of its frequency in later childhood, which suggests that the potentiality for sickling is incompletely developed at birth. Of 226 negro mothers, 18 (8 per cent.) showed sicklaemia, and in those affected the percentage of red cells sickling was usually 100 and exceeded 84 in every case. Of their 226 newborn infants, 19 (8·4 per cent.) showed sicklaemia, and in the affected infants the maximum sickling varied from 0·5 to 29·5 per cent. of the red cells, with a mean of 11 per cent. Sickling of the infants' red cells often required 48 hours to reach a maximum, instead of the 24 hours which usually sufficed for the mothers' red cells. Presumably a lower oxygen tension is required to sickle infants' cells, and as there is a significant shift to the left of the oxygen dissociation curve of oxyhaemoglobin at birth which only gradually reaches adult values at the age of six weeks, the longer period necessary for sickling in the newborn may be due to a greater affinity of foetal haemoglobin for oxygen compared with the adult type of haemoglobin. This would not, however, account for the low percentage of sickled red cells in newborn infants, since the maximum percentage of sickling could not be raised by use of a gas chamber method in which oxygen was excluded entirely from the system. Simple immaturity of the cells is not a sufficient explanation either, because although normoblasts and reticulocytes sickle less readily than mature erythrocytes, the blood of the infants contained no high percentage of immature cells. There is, however, evidence that human foetal haemoglobin differs chemically from adult haemoglobin, probably in the chemical structure of the globin. It is suggested that foetal haemoglobin is unable to produce sickling, and that the sickling trait and the percentage of red cells showing the sickling trait progressively increase as red cells containing the adult type of haemoglobin are produced. The foetal haemoglobin disappears at the age of about 4½ months, and the life span of the erythrocytes is about 4 months, so that if adult haemoglobin began to develop at birth, four months would elapse before it would entirely replace the foetal haemoglobin. One infant observed over such a period developed 90 per cent. sickling at 4½ months compared with only 6 per cent. sickling at birth. Normally an oxygen tension of 45 mm. Hg is the threshold for sickling, and consequently the lower oxygen tension that occurs *in utero* should cause complete sickling and thus be incompatible with life. There are, however, no records of the pathological findings of sickle cell anaemia in autopsies of newborn or stillborn infants. It seems, therefore, that the foetal haemoglobin lacking the sickling property of adult haemoglobin, prevents the automatic extinction of sickle cell disease from deaths *in utero*, and partially protects the infant during the first four months of life during which time the foetal haemoglobin gradually disappears from the blood. *F. Murgatroyd*

VALENTINE, W. N. & NEEL, J. V. **A Statistical Study of the Hematologic Variables in Subjects with Thalassemia Minor.** *Amer. J. Med. Sci.* 1948, v. 215, No. 4, 456–60, 3 figs. [13 refs.]

Cooley's anaemia, an inherited haematological disorder of people of Mediterranean stock, may be severe, progressive and almost invariably fatal, or relatively mild; it is suggested that the terms thalassaemia major and thalassaemia minor be applied respectively to the two types. The major variety occurs in about 1 in 2,400, while the minor variety occurs in 1 in 25 births to persons of Southern Italian or Sicilian stock in Rochester, New York. The minor variety occurs in well-nourished persons with hypochromic microcytic erythrocytes, which are frequently oval or appear as target cells; basophilic stippling is common. Haemoglobin and haemocrit values are usually but not invariably low, and by comparison the total number of erythrocytes is disproportionately high. The erythrocytes show increased resistance to haemolysis by hypotonic saline. There may or may not be leucocytosis, reticulocytosis and elevated icterus index, or splenomegaly. In 82 persons with thalassaemia minor, there was an average deficiency of 2 to 3 gm. of haemoglobin per 100 cc. of blood, the defect being superimposed on the normal levels of haemoglobin for male and female so that the males showed higher haemoglobin values than did the females similarly affected. The tendency for persons with thalassaemia minor to have relatively elevated erythrocyte counts was confirmed, only 2 out of 58 of the adult patients having erythrocyte counts below 5 million per cmm.; in 48·3 per cent. of thalassaemic females and in 85·8 per cent. of thalassaemic males the counts were above 5½ million per cmm., while 57 per cent. of the males had counts above 6 million per cmm. The mean corpuscle volumes and mean corpuscular haemoglobin values were markedly below normal. The mean corpuscular haemoglobin concentrations were not so markedly lowered, showing that although the red cells are small in volume, each cell for its volume is only moderately deficient in haemoglobin. *F. Murgatroyd*

STOWE, M. **Report on Anaemia amongst the Women of Bhopal.** *J. Ass. Med. Women in India.* 1948, Feb.–May, v. 36, No. 1, 5–20, 5 graphs.

VENOMS AND ANTIVENENES

CECCALDI, J. & TRINQUIER, E. Recherches sur la toxicité des glandes salivaires de divers Colubridés aglyphes et opistoglyphes africains. [**Study of the Toxicity of the Salivary Glands of different African Aglyph and Opisthoglyph Colubrines.**] *C. R. Soc. Biol.* 1948, Apr., v. 142, Nos. 7/8, 440–41.

The authors studied the toxicity of the salivary glands of 8 species of Aglypha and 8 of Opisthoglypha by injecting saline suspensions of the macerated glands into mice in successive dilutions. All the Aglypha except one killed less than 4 mice and that one killed 8: 5 of the 8 Opisthoglypha killed respectively 16, 32, 80, 320 and 5,120 mice. Two species of Opisthoglypha killed less than 4 mice and one killed 8.

The Aglypha studied are not likely to be harmful to man. On the other hand, certain of the Opisthoglypha investigated seem capable of causing fatal accidents in man. This applies especially to *Dipsadomorphus blandingii*, which killed 320 mice in the tests and *Elapops modestus* which killed 5,120.

H. J. O'D. Burke-Gaffney

TRINQUIER, E. & CECCALDI, J. Toxicité des glandes salivaires chez quelques Vipéridés africains à leur naissance. [**Toxicity of the Salivary Glands of some African Vipers at Birth.**] *C. R. Soc. Biol.* 1948, Apr., v. 142, Nos. 7/8, 441.

It is known that new-born venomous snakes have well-developed salivary glands and venom comparable with that of adults; but few investigations are recorded on quantitative studies, particularly in African snakes.

The authors investigated this point in the new-born of two species, *Bitis gabonica* and *Bitis nasicornis*. Successive dilutions of saline emulsions of the glands were injected into mice.

In the case of *B. gabonica*, emulsions from 2 glands were enough to kill 640 mice, but not 1,280: the venoms were lethal for at least 11 kgm. of animal. Similar emulsions from new-born *B. nasicornis* killed only 4 mice; its venom was thus far less toxic than that of *B. gabonica*.

These differences were maintained in adult life: experiments showed that venom from a large adult specimen of *B. gabonica* was lethal to mice at the order of 485 kgm. of animal, while in the case of *B. nasicornis* the figure was 110 kgm. *H. J. O'D. Burke-Gaffney*

CONSTANT, Y. & GOUÈRE, P. Sur les phénomènes d'aranéisme provoqués par *Latrodectus menavody*. [**Symptoms of Bites by** *Latrodectus menavody*.] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 3/4, 234–7.

The specific name *menavody* was given to this spider because it is a Madagascar word indicating "red spots behind." Bites by it are generally dreaded by both indigens and by Europeans. Detailed accounts of three cases are given; one patient was bitten on the inside of the left thigh, one on the right instep, and one on the back. The symptoms in the first and third were similar: pain at first local but soon extending widely over the body but greatest in the legs, no loss of reflexes, profuse sweating, retention of urine, albumin present in the small amount which may be passed, and a little blood, an urticarial pruriginous rash on the 3rd or 4th day, slight rise of temperature at first, later falling below normal, and recovery in 5–6 days. In the second patient the early symptoms were the same, but signs of cardiac failure set in and in spite of all the remedies tried death occurred 27 hours after the infliction of the bite. No work has yet been done on the venom of this spider and treatment at present is purely symptomatic, to ease the pain, check the sweats and combat the failing heart. *H. Harold Scott*

DERMATOLOGY AND FUNGUS DISEASES

CROSS, F. W. **The Effect of Hydrogen-Ion Concentration on the Yeastlike Phase of** *Histoplasma capsulatum* **(Darling).** *Pub. Health Rep.* Wash. 1948, June 4, v. 63, No. 23, 739–46, 2 figs. [10 refs.]

The purpose of the author's experiments was to find a liquid medium suitable for the propagation of *Histoplasma capsulatum* in its pure, smooth, yeast-like form. Five strains of the fungus were tested for growth on three different media over a wide range of *p*H, at incubation temperatures of 25°C. and 37°C. (The fungus cannot vegetate in the yeast form at 25°C. on any medium.)

The following results refer to cultures incubated at 37°C.: On a glucose (1 per cent.) broth medium the yeast form showed a marked tendency to revert

to the mycelial form under all conditions of the test, so this medium was discarded as unsuitable. On beef-extract-broth the best results were obtained at the hydrogen-ion concentration of *p*H. 7·3, but in the higher and lower *p*H ranges there was a slight but increasing tendency to develop rudimentary mycelium. "Difco" brain-heart-infusion-broth proved the most satisfactory medium, with optimal conditions in the *p*H range 7·4 to 7·5, but again in the higher and lower *p*H ranges there was a tendency towards reversion to the mycelial form; this was greater in the lower *p*H range, but in the higher range it was accompanied by retardation of the growth of the yeast form.

J. T. Duncan

Rawson, A. J., Collins, L. H., Jr. & Grant, J. L. **Histoplasmosis and Torulosis as Causes of Adrenal Insufficiency.** *Amer. J. Med. Sci.* 1948, Apr., v. 215, No. 4, 363–71, 5 figs. [25 refs.]

A tabular analysis is given of eight previously published cases of histoplasmosis (*Histoplasma capsulatum*) in which necrosis of the adrenal glands induced symptoms of adrenal insufficiency, and eleven other cases of histoplasmosis and one of torulosis (*Cryptococcus* [*Torulosis*] *neoformans*) in which the adrenal glands were involved without symptoms of adrenal insufficiency, are noted. This is followed by detailed reports of the ninth case of adrenal insufficiency due to massive necrosis of the adrenals by *H. capsulatum*, and a case, claimed as the first, of torulosis characterized by adrenal insufficiency. The latter was only diagnosed as torulosis at post mortem examination. In both patients, who were women aged 62 and 41 years, respectively, excessive weakness was the first symptom.

Attention is drawn to the fact that in the cases of adrenal failure due to *H. capsulatum*, the ratio of 2 males to 1 female is the same as that noted in Adamson's disease from all causes although the age group (39 to 63) is somewhat higher than that for Adamson's disease (30 to 50). *G. C. Ainsworth*

Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. G., Beard, R. R. & Saito, Margaret T. **The Use of Coccidioidin.** *Amer. Rev. Tuberculosis.* 1948, Apr., v. 57, No. 4, 330–60, 2 figs. [56 refs.]

This detailed study of coccidioidin and its diagnostic use should be read in the original. After dealing with the relatively crude preparations of coccidioidin used in the earlier work on coccidioidomycosis, the authors recommend the method of preparation in common use in the United States at the present day. This consists in growing selected strains of *Coccidioides immitis* for 2 months at 22°C. in a modification of the synthetic, liquid, asparagine medium devised for the production of tuberculin. The culture liquid is then filtered through a Seitz filter and the sterile filtrate, preserved with 1 : 10,000 merthiolate, constitutes the stock coccidioidin. As the asparagine medium does not cause dermal reactions, test control injections are not necessary.

The active principle of coccidioidin, which is mainly or entirely of polysaccharide nature, although a small amount of apparently non-protein nitrogen is always present, is extremely stable and will withstand a temperature of 120°C. in the autoclave for 10 minutes, or flowing steam for an hour. If sterile and undiluted, it can be kept in cold storage for an indefinite time without loss of potency and, in fact, a sample left at air temperature in a warm climate for nearly 9 years was found to be fully potent for the skin test. Even when diluted to 1 : 100, it can safely be kept in cold storage, but bacterial contamination may render it inert or may even cause it to give spurious positive reactions.

Coccidioidin should be standardized by intradermal tests on known human reactors, non-reactors and equivocal reactors. The test dosage recommended is 0·1 ml. intradermally, of a 1 : 1,000 dilution for active, early cases, or down to 1 : 10,000 if erythema nodosum, indicating high sensitivity, is present ; in the disseminated disease, in which sensitivity may be very low or absent, a 1 : 10 dilution may be necessary, and for epidemiological survey work a 1 : 100 dilution may be used on the average. The reaction is sufficiently specific for its purpose and it is of the delayed type, like the tuberculin reaction. It is nearly always discernible at 24 hours, reaching its maximum at about 36 hours, but it may develop earlier or later and, therefore, interval readings should be taken. Dermal sensitivity to coccidioidin cannot be induced passively by injecting the serum of a reactor into the skin of a non-reactor, nor does the skin become sensitized by the repeated injection of even strong doses of coccidioidin into the skin of a non-sensitive subject, although he may become sensitive later from a natural infection. Dermal sensitivity usually appears a few weeks after infection, but its onset may be delayed. It may be of only transient duration, but it usually lasts for many years. *J. T. Duncan*

NABARRO, J. D. N. **Primary Pulmonary Coccidioidomycosis. Case of Laboratory Infection in England.** *Lancet.* 1948, June 26, 982–4, 2 figs. [28 refs.]

See *Bulletin of Hygiene*, 1948, v. 23, 688.

RUSSO, E. & GOMES, R. P. Novas observações de esporotricose. [**Fresh Observations on Sporotrichosis.**] *Hospital.* Rio de Janeiro. 1948, Feb., v. 33, No. 2, 215–22, 9 figs.

Four cases are briefly recorded ; one, a girl of 8 years, with a warty lesion of the right cheek ; one, a girl of 17 years, with a lesion of the left hand between the thumb and forefinger ; third, a boy of 12, with lesions of the left hand and forearm ; the fourth, an adult woman with a small lesion on the ulnar side of the base of the right little finger and later two others near the cubital fossa.

The chief interest of the paper, however, is that all were diagnosed by isolation of *Sporotrichum schenckii* grown on Sabouraud dextrose forming a blackish pigment. On transfer to ordinary agar, *p*H 6·6, it grew well but white, with no pigment at all and continued to do so on this medium. When, however, it was retransferred to Sabouraud's medium again it again assumed the coloured growth. *H. Harold Scott*

HEAT STROKE AND ALLIED CONDITIONS

STEWART, W. **Effects of Heat with special reference to its Occurrence in British Troops in the Persian Gulf Area in 1941–42.** *J. Roy. Army Med. Corps.* 1948, May, v. 90, No. 5, 178–93, 3 figs. [16 refs.]

In the summer of 1942 there were 168 cases of heat stroke, with 32 deaths, and 1,955 cases of heat exhaustion, with 13 deaths, among the British troops in the Persian Gulf area ; 14·9 per cent. of the total British strength was affected. The author gives a brief description of these cases, and considers them in relation to recent work on the physiology of man in the heat, and on the pathological changes found in men suffering from the effects of heat.

The author distinguishes four types of heat effects : (1) Heat exhaustion, (2) Subacute effects of heat, (3) Heat cramps, and (4) Acute heat stroke. The

line of distinction between the first three is difficult to draw; but subacute effects, if untreated, may develop into heat stroke, which is acute hyperpyrexia.

Immediate treatment is essential with controlled replacement of water and salt, and, for hyperpyrexia, active cooling. The importance of suitable clothing, adequate rest, proper acclimatization and a sufficient intake of salt and water in avoiding heat casualties is emphasized. Periodic medical examinations of all those serving in hot areas is advised.

[This paper would serve as a useful introductory review of the subject, but it adds nothing to our knowledge of heat effects. The author's classification of the different types of effects of heat is not universally accepted; it is the same as that given in the official memorandum reviewed in this *Bulletin*, 1944, v. 41, 74.] *W. S. S. Ladell*

MISCELLANEOUS DISEASES

COUTINHO, A. Eosinofilia tropical. [**Tropical Eosinophilia.**] *Hospital.* Rio de Janeiro. 1948, Jan., v. 33, No. 1, 77–85. [25 refs.]

The author records five cases which presented the symptoms of tropical eosinophilia—asthmatic attacks, eosinophilia ranging from 56 to 71 per cent. in a leucocytosis from 12,000 to 26,500 per cmm. Unfortunately these records make confusion worse confounded rather than elucidate this vexed question. Each of the cases is given in detail; one disappeared and could not be followed up, the others cleared up under different forms of treatment. Two were suffering from amoebiasis and were treated with emetine, enterovioform and carbarsone; another, a medical man, seemed to be an ordinary case of bronchial asthma which cleared up with ascorbic acid and calcium. The only positive finding here was a strong reaction to tuberculin, 1 : 10,000. The remaining patient improved on penicillin and sulphadiazine, but still suffered with slight attacks of nocturnal asthma and was given an autogenous vaccine of *N. catarrhalis*, *Pneumococcus* and *H. influenzae* and improved markedly when abdominal pain elicited the fact that he had a duodenal ulcer. On the idea of a possible Löffler's syndrome he was given arsenicals and the dyspnoeic attacks disappeared completely though he still had some stertor. [An interesting series of cases, but leaving the subject as obscure as before.] *H. Harold Scott*

FERRO-LUZZI, G. Studio sui fenomeni di malnutrizione in Eritrea. Nota II. [**Malnutrition in Eritrea.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1947, v. 7, Nos. 5/6, 483–94, 1 fig. English summary.

This article is an informative and interesting account of a disease known for many years (the author says "for centuries") among those consuming the seeds or flour made from the seeds of a plant known as "seberè." It grows on the upper levels and is abundantly cultivated and used fresh or cooked, alone or with other kinds of flour for making cakes (*chiccià*) which are eaten by all and sundry. It is cheap, easily cultivated, needs little water and is not liable to damage by acarides. Usually only a small proportion is used, mixed with other flour, but at times when other flour is scarce the proportion is higher. This happened after an invasion by locusts in 1946. If more than 50 per cent. of the flour is used for making these cakes symptoms appear in 20–100 days according to the quantity eaten.

Seberè was identified as *Lathyrus sativus*; some samples are adulterated with *Vicia sativa*, but samples sent to the Agricultural Department of Eritrea were

not so adulterated. The symptoms were those of spastic paraplegia characteristic of lathyrism and affected males and females and all ages, but more particularly the poorer classes who consumed this flour in larger quantities. Details are given of six patients and an illustration of one of them showing the attitude and gait of typical spastic paraplegia. Five were males, aged 7, 8, 17, 25 and 33 years, and one woman aged 30. There was no disturbance of vision, no psychic symptoms, no change in the cerebrospinal fluid. Very rare was any affection of the upper limbs or of the sphincters. Avitaminosis did not seem to play any part primarily, but it may aggravate the basic lathyrism; the administration of vitamins had no curative effect. Prophylactic measures are obvious, but attempts at cure have altogether failed.

H. Harold Scott

Bloss, J. F. E. **Symmetrical Gangrene in an African.** [Correspondence.] *Brit. Med. J.* 1948, July 3, 52.

A fatal case in a Sudanese aged 35 [see this *Bulletin*, 1947, v. 44, 937].

Burkitt, D. P. **Spontaneous Rupture of the Spleen.** *East African Med. J.* 1948, Apr., v. 25, No. 4, 167–74. [22 refs.]

A review of the causes.

PROTOZOOLOGY: GENERAL

Bijlmer, J. **On the Recovery of Protozoa and Eggs of some Species of Helminths in Human Feces.** *J. Parasitology.* 1948, Apr., v. 34, No. 2, 101–7. [10 refs.]

[See this *Bulletin*, 1947, v. 44, 1101.]

Seaman, G. R. **Penicillin as an Agent for Sterilization of Protozoan Cultures.** *Science.* 1947, Oct. 3, 327.

The author concentrated *Colpidium campylum* by centrifugation and washed the organisms three times with sterile Hahnert's solution (*Phys. Zool.*, 1932, v. 5, 491). A few drops of this washed concentrate were added to 3 per cent. sterile Difco proteose-peptone solution containing 5,000 units of penicillin/cc. After 12 hours in the penicillin solution, the organisms were transferred through three successive washes of 3 per cent. proteose-peptone. A drop containing the organisms and the fluid from the last wash was plated on agar: in 8 tests, no bacterial growth was seen and the colpidia were apparently uninjured by 12 hours' exposure to this concentration of penicillin.

It seems that this method may be used to obtain sterile cultures of most protozoa, but the survival time of each species of organism in a given concentration of penicillin must be ascertained separately: if this time is very short, lower concentrations are required. Preliminary tests suggest that *Paramoecium nucleatum* remains vigorous for 5 hours in a solution of 5,000 units of penicillin/cc., but is killed in 12 hours at this concentration. It is added that the process does not require constant attention, large numbers of organisms are recovered and the number of transfers is reduced to a minimum.

H. J. O'D. Burke-Gaffney

Tedeschi, G. G. Attività antiprotozoaria di un pigmento estratto dall' *Aspergillus niger*. [**Antiprotozoal Action of a Pigment from** *Aspergillus niger*.] *Riv. di Parassit.* Rome. 1948, Mar., v. 9, No. 1, 5–9. English summary (4 lines).

In the author's laboratory a strain of *Aspergillus niger* was isolated from a culture contaminated by it. It was found to produce a pigment having very

definite action on certain protozoa. On further study a method of extraction of this pigment was devised. The mould was cultivated on a liquid Sabouraud's medium in a Roux flask at 30°C. till it had developed fully. The growth was then removed very carefully to avoid damaging it and detaching the spores, and was then placed to dry at a temperature of 40°C. When completely dried it was extracted with chloroform in a Soxhlet apparatus till the extracting solvent came away colourless. When concentrated the solution had a deep yellowish-brown colour ; it was allowed to cool and treated repeatedly with phosphate solution at *p*H 7·5 when it became yellow. The chloroform was then driven off and the product brought to *p*H 3 with HCl or H_2SO_4 ; a flocculent precipitate formed and on centrifuging a greenish-yellow product was obtained which was repeatedly washed with distilled water, brought up to *p*H 6, then dried, and NaOH cautiously added to obtain a clear liquid of an intense brown colour at *p*H 2·5.

Testing this, the author found that it had no action on *Bact. coli*, very little on *Staph. pyogenes aureus*. It was haemolytic but not if serum were present ; in fact, haemolysis could be prevented by addition of serum. On protozoa the following results were observed : *Polytoma uvella* (a flagellate) was fixed at once ; *Paramecium* was immobilized but not permanently ; *Hartmanella hyalina*, a coprozoic amoeba, was immobilized with extended pseudopodia ; *Giardia enterica* [? *intestinalis*] moving in liquid faeces was immobilized and killed. *Trypanosoma lewisi* and *T. gambiense* in blood were rapidly immobilized. It was active on these also when injected into experimental animals, white rats and guineapigs, in a dose of 3 cc. of the solution per 100 gm. body weight, and apparently caused no systemic disturbance. *H. Harold Scott*

ENTOMOLOGY AND INSECTICIDES : GENERAL

Laird, M. **A Method of securing Living Mosquitoes to Mounts in Studies of Problems concerning Flight.** *Science.* 1948, June 18, 656, 1 fig.

Abraham, O. K. *Anopheles* (*Anopheles*) *kyondawensis* **n.sp. from Lower Burma.** *Med. J. Malaya.* 1947, Mar., v. 1, No. 3, 173–6, 5 figs.

Neri, I. Osservazioni morfologiche sul pretarso delle culicine. [**A Morphological Observation on the Pretarsus of a** *Culex*.] *Riv. di Parassit.* Rome. 1948, June, v. 9, No. 2, 93–6, 2 figs.

The English summary appended to the paper is as follows :—

" The author reports the description of a peculiar organ present in the pretarsus of *Culex pipiens autogenicus*."

Macfie, J. W. S. **Some Species of** *Culicoides* **(Diptera, Ceratopogonidae) from the State of Chiapas, Mexico.** *Ann. Trop. Med. & Parasit.* 1948, Apr., v. 42, No. 1, 67–87, 10 figs.

The author has examined a portion of a large collection of Ceratopogonidae estimated to contain 20,000 specimens. Most of the material was collected by Dr. A. Dampf from May to July, 1935, in Mexico.

The portion examined includes 3,335 specimens of *Culicoides* of which 97 per cent. were *C. guttatus*. (It was in specimens of this species that Dr. Dampf found developing filariae in 1936.) The remaining 3 per cent. contained sixteen other species ; ten of them are new and are described in this paper. A key is

given for the identification of some sixty species of *Culicoides* (females) likely to be found in the Caribbean area, including also species occurring in regions ranging from southern Mexico to Brazil. *H. S. Leeson*

THEODOR, O. **Classification of the Old World Species of the Subfamily Phlebotominae (Diptera, Psychodidae).** *Bull. Entom. Res.* 1948, May, v. 39, Pt. 1, 85–115, 15 figs. & 2 pls. [33 refs.]

The present paper is a valuable review of the systematics of the sand flies (*Phlebotomus*) of the Old World, written by an authority on the subject. These insects have not been monographed since the paper by LARROUSSE [this *Bulletin*, 1921, v. 18, 196]. At that time 32 species and 8 varieties were known: the present author deals with 127 species and 34 varieties, of which he has seen the greater part himself.

It might be said that some previous workers on the subject have tended to be "Phlebotomists" rather than Dipterists, for they have developed a terminology in connexion with sand flies alone, with little regard for terms which are used for the Diptera generally. The present author takes account of comparative anatomy which will entail a few alterations in the use of technical terms. With regard to "buccal cavity" and "pharynx" he is conservative, basing his view on the work of SNODGRASS (*Principles of Insect Morphology*, 1935. McGraw-Hill, New York): he does not accept "pharynx" and "oesophageal pump", terms put forward by JOBLING [this *Bulletin*, 1928, v. 25, 825] for certain structures in *Culicoides* which are plainly identical with those in *Phlebotomus*.

The earliest clear reference to these insects is that made by Scopoli in 1786. The growth of knowledge since that time and the earlier systems of classification are here reviewed, and on a basis of this earlier work, much of which is still valuable, the author puts forward his own views. He classes *Phlebotomus* and the other blood-sucking genera immediately related to it, as a sub-family, the Phlebotominae, of the family Psychodidae. In doing this he rejects a proposal made by ADLER and himself [this *Bulletin*, 1930, v. 27, 89] to create a separate family for the blood-sucking forms, and we are glad to see that he has done so. The other three sub-families of the Psychodidae contain no biting forms (the record of biting by *Pericoma townsvillensis*, Taylor, 1915, being rejected).

The Phlebotominae are divided into four genera, *Phlebotomus*, *Sergentomyia*, *Lutzomyia* and *Brumptomyia*. Of these the last two are exclusively American; the first two, with which this paper is concerned, are characterized on the following points, among others:—

Phlebotomus Rondani, 1843.—Species without armature in buccal cavity. Pharyngeal armature generally similar in male and female. Hairs on dorsum of abdomen mostly in erect tufts. Spermatheca completely or incompletely segmented. This genus contains nearly all the species which feed on mammals, and all those which are implicated in the transmission of human infections.

Sergentomyia França and Parrot 1920.—Species with a buccal armature; marked sexual dimorphism in buccal and pharyngeal armature. Spermatheca generally smooth or crinkled tubes or capsules: incompletely segmented in a few forms. Only a few members of this genus are known to bite man (*S. schwetzi*, *africana* and *babu*): it is known that some feed on birds and reptiles.

The author defines a number of sub-genera, some of which are new, both in *Phlebotomus* and *Sergentomyia*, naming the type species of each and providing a key to the sub-genera. The paper concludes with a list of all the Old World

species and authorities with a few words on the geographical distribution of each. A number of names are sunk as synonyms for reasons not given here. The paper is concluded with a list of works " concerned with classification " and with two excellent plates of photomicrographs showing characteristic details of structure. *P. A. Buxton*

THEILER, Gertrud. **Zoological Survey of the Union of South Africa. Tick Survey—Part I.** *Onderstepoort J. Vet. Sci. & Animal Industry.* 1948, Mar., v. 23, Nos. 1/2, 217–31, 4 folding coloured maps.

ACOSTA BAYARDO, R. Informe preliminar acerca de infestación por niguas o *Tunga penetrans* en el Estado de Nayarit. [**A Preliminary Note on Infestation by *Tunga penetrans* in the State of Nayarit.**] *Medicina.* Mexico. 1948, June 25, v. 28, No. 558, 251–3.

ARDRAN, G. M. **Armillifer Armillatus. A Note on Three Cases of Calcification of the Cysts in Man.** *Brit. J. Radiol.* 1948, July, v. 21, No. 247, 342–5, 6 figs. [17 refs.]

The diagnosis of porocephalosis in the living subject is rare, but cases have been reported from time to time ; most of these have been concerned with calcified nymphs of *Armillifer armillatus*, which probably do not produce symptoms as a rule, but cases in which pathological effects were noted have been recorded [this *Bulletin*, 1947, v. 44, 136, 626].

The present author, from the Royal Liverpool United Hospital, discusses this form of infestation and refers briefly to the literature. He then records three cases in which multiple calcified nymphs were demonstrated radiographically in natives of West Africa.

The first patient was complaining of pain in the back and osteoarthritic changes were found in the spine. Very many calcified nymphs of *A. armillatus* were demonstrated in the abdominal cavity and there were one or two in the upper zone of the right lung. It is not considered that the symptoms were due to the presence of the nymphs. The second patient had suffered from a cough and pain in the chest for a month : radiography showed numerous calcified nymphs over both lung fields. The third case had similar symptoms and radiological appearances.

All these findings are illustrated with X-ray photographs in the text. When the nymphs are seen *en face* they are unlike any other calcification, but when seen " end on " over a muscle area, they might easily be confused with the cysts of cysticercosis. Atypical forms might be confused with calcified glands, calculi and the like, but calcified tuberculous foci are not common in natives of West Africa.

The author refers to the paucity of information regarding such calcified nymphs in the standard text books : and he stresses the need for keeping the condition and its features in mind. Once it has been seen, it will not readily be forgotten ; and after the first of his cases had been recognized there was no difficulty in identifying the others.

The living larvae may be another cause for transient pneumonias and haemoptyses. The author suggests that a skin test might be developed to detect the living parasite. It is likely that with an extension of radiographic services in the tropics, more cases will come to light.

The author's present three cases bring the total record of radiographically demonstrated cases up to five. *H. J. O'D. Burke-Gaffney*

PATTON, R. L. & SARKARIA, D. S. **Preparation of Standard Films of DDT Crystals for Toxicity Studies.** *Science.* 1948, June 18, 654, 1 fig.

See also p. 884, HERTIG & FAIRCHILD, **The Control of Phlebotomus in Peru with DDT.**

HADJINIKOLAU, J. & BUSVINE, J. R. **Toxicity of Limewash containing DDT or " Gammexane " to Mosquitos** (*Aedes aegypti*, **L.).** *Bull. Entom. Res.* 1948, May, v. 39, Pt. 1, 179–83, 1 fig.

In many rural malarious districts, the dwellings have mud or plaster walls, brightened by an annual coat of whitewash. The object of the tests described was to investigate the feasibility of incorporating DDT or *gamma* BHC in limewash to give a residual action against mosquito adults.

The tests were done in one-foot-cube cages, each with a sleeve and window in the front to introduce and watch the insects. The walls, which were removable, were made of pieces of Essex board one foot square ; this is an absorbent material offering difficulties to applying residual films of insecticides. The Essex boards could be treated in various ways and applied to the cage framework for test. Mosquitoes were introduced for various periods of exposure and then removed to a clean cage ; the mortality was determined after twenty-four hours. During the " exposure", mosquitoes were free to fly or to settle on the untreated portions of the cage, which comprised about forty per cent. of the total internal surface. *Aëdes aegypti* were used as the test insects on account of the ease in producing large numbers in the laboratory throughout the year.

The experiments were made with applications to the walls of a DDT wettable powder mixed with lime to give a white wall coating, and this treatment was compared with DDT applied in kerosene solution at the same rate (160 mgm./sq. ft.). In the whitewash application an eventual mortality of 85–90 per cent. was obtained after an exposure of two hours ; the results with the kerosene solution application were inferior. Equally high kills were obtained with much lower rates of *gamma* BHC (8 mgm./sq. ft.) applied in a wettable powder mixed with limewash.

Repeated tests made at intervals indicated that both the DDT and *gamma* BHC " whitewash " applications remained highly effective up to about 6–8 weeks under temperate conditions. A higher rate of *gamma* BHC (40 mgm./sq. ft.) gave a complete kill with a one-hour exposure after twenty-two weeks interval. The DDT treatment was not tested after eight weeks until seven months, at which point it showed signs of deterioration. *J. R. Busvine*

LABORATORY PROCEDURES

GALL, D. **A Simple Technique for the Microscopy of Living Tissues** ***in situ*****, with some Observations on the Splenic Circulation.** *Ann. Trop. Med. & Parasit.* 1948, Apr., v. 42, No. 1, 54–66, 1 diagram. [43 refs.]

A detailed description is given of a technique suitable for microscopic observation of the circulation at the surface of exposed organs. The paper is concerned with experiments on mice and observations on the spleen. The tip of the organ is exposed through an abdominal incision, covered with a cover-slip and the exposed surfaces bathed with warm Tyrode solution kept at a constant temperature and rate of flow. Illumination of the surface is produced by a 24-watt filament source focussed on the end of a glass rod.

Experience is necessary to overcome the interruption of vision due to respiratory movements, and to interpret the observations on circulatory changes. The author suggests that the flow through the splenic pulp of mice is by tortuous channels, constant in position, and ramifying between the splenic cells. There is no evidence for a closed circulation.

All observations may represent the normal modified by anaesthesia, exposure, disturbance of surface pressure, temperature etc. The illumination used is insufficient for the photography of moving tissues. *E. T. Renbourn*

REPORTS, SURVEYS AND MISCELLANEOUS PAPERS

WORTH, H. I. **The Age Question among Asiatic Girls in Malayan Courts of Law.** *Med. J. Malaya.* 1947, June, v. 1, No. 4, 252–71.

European standards on height, weight, centres of ossification and date of onset of puberty are not applicable to Asiatic girls in Malaya. "Asiatics" could not be grouped together, racial groups showed differences, especially the three main groups—Chinese, Indians and Malays.

Nine tables are furnished showing the average and maximum and minimum heights and weights of the four main groups examined, as well as of some of the minor groups, arranged according to ages from 5 years to 19 years. The conclusion is drawn that the European standard of height and weight is higher than that of any of the Asiatic races in Malaya ; a greater difference is noted in the weight than in the height and there is a much greater range in the weight of Asiatics but a smaller range in the height.

Onset of menstruation tended to be earlier in the local Asiatic groups than in Europeans.

The date of eruption of permanent teeth appeared to be earlier among Asiatic races. No deciduous teeth were found at the age of 12–13 years, the lower second molar was seen in all those examined at that age and the whole lower set was present, excluding the third molar. Earlier eruption of the canine teeth was also noticeable.

Details should be consulted in the original by all those interested in medico-legal work in tropical countries. *P. A. Clearkin*

MÉGROZ, R. L. **Ronald Ross as Medical Discoverer and Poet.** *J. National Malaria Soc.* 1948, June, v. 7, No. 2, 85–94, 2 figs. & 1 pl.

BOOK REVIEW

SERGENT, Edmond & SERGENT, Etienne. **Histoire d'un marais algérien.** [The History of an Algerian Marsh.] 293 pp., 18 pls., 3 folding maps & numerous text figs. 1947. Alger : Institut Pasteur d'Algérie.

In 1911 the authors with Dr. E. Roux were motoring along the Mitidja Plain. They passed a derelict farm that had had a tragic history—a promising enterprise that had been brought to disaster by malaria. That experience prompted Dr. Roux's suggestion that the Pasteur Institute of Algiers should seek out some similar place, not too far from the Institute, that malaria had made uninhabitable. It should be reclaimed, freed from its malaria and brought back into cultivation, as a practical demonstration of what recently acquired

knowledge of the epidemiology of malaria might accomplish. Dr. Roux promised to provide the funds necessary for the acquisition of such a property. The 1914–18 war intervened and it was only in 1927 that the Pasteur Institute obtained possession of land in every way suitable for the purpose of the experiment, 360 hectares of marshland in the Mitidja Plain, 25 km. south-west of Algiers, the *Marais des Ouled Mendil*. Malaria had made it uninhabitable; piroplasmosis had prohibited its use as a grazing ground.

The *Histoire d'un Marais Algérien*, a charming volume, describes that marshy waste as it was, and gives a graphic account of the measures that, step by step, succeeded in transforming it into a malaria-free flourishing agricultural property. Today it is a very valuable adjunct to the Pasteur Institute of Algiers. Colmatage, drainage, road-making, tree planting, farm building, agriculture, well-sinking were all systematically taken in hand. Forty-six Europeans have dwelt in that once malaria-infested spot, the average length of stay being four years; all remained free from malaria infection. European cattle, vaccinated against piroplasmosis, thrive.

This great achievement is very worthily commemorated in this lyrical volume enriched with delightful illustrations and innumerable apt quotations. The history is much more than a record of achievement. It provides interesting information about Algerian history, ancient and modern, archaeology, geology, fauna, flora, man's tribute to malaria, the history of malaria research, and antimalarial methods. Its perusal is a pleasure to which the wealth of apt quotations from the classics contributes much. *Norman White*

We record with the greatest regret the deaths of Lt.-Colonel W. F. Harvey and Dr. C. M. Wenyon.

Lt.-Colonel Harvey, who died in Edinburgh on September 11, 1948, contributed abstracts of bacteriological papers to the *Tropical Diseases Bulletin* from 1925 onwards, and was later sectional editor for cholera and plague up to the time of his death.

Dr. Wenyon died in London on October 24, 1948. He was editor of the *Kala Azar Bulletin* in 1911, and subsequently, for the last 36 years, was sectional editor of the *Tropical Diseases Bulletin* for leishmaniasis and protozoology.

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ALPHABETICAL LIST OF AUTHORS OR SOURCES

Abraham, O. K., (933).
Acosta Bayardo, R., (935).
Afridi, M. K., 862.
Allaart, P. J., 903.
Anderson, H. H., Johnstone, H. G., Packer, H., Young, J. D., Callison, M. K., Hambly, A. S., Jr., Anderson, J. van D. & Reed, R. K., 903.
Ardran, G. M., 935.
Ashworth, R. de B., Crowther, A. F., Curd, F. H. S. & Rose, F. L., (866).
Awny, A., 899.

Baldwin, E., 921.
Berberian, D. A., 870.
Berry, E. G., 913.
Bettini, S., 861.
Bieling, R. & Oelrichs, L., 886 *bis*, 892, 893.
Bijlmer, J., (932).
Black, R. H., 873.
Blanc, G., Bruneau, J., Poitrot, R. & Delage, B., 892.
Bloss, J. F. E., (932).
Bolliger, A. & Backhouse, T. C., 883.
von Bonsdorff, B., 920.
Bovet, D., Decourt, P., Schneider, J. & Montezin, G., (873).
Bozicevich, J. & Hoyem, H. M., 916.
Brown, E. H., 907.
Burkitt, D. P., (932).
Burrows, W. & Havens, I., 898.

Ceccaldi, J. & Trinquier, E., 927.
Chang, N. C. & Hou, T. C., 882.
Cliffe, W. H., Curd, F. H. S., Rose, F. L. & Scott, M., (866).
Collier, W. A., 909.
Constant, Y. & Gouère, P., 928.
Corradetti, A., 871.
Coutinho, A., 931.
Coutinho, J. de O., (857).
Craige, B., Jr., Whorton, C. M., Jones, R., Jr., Pullman, T. N., Alving, A. S., Eichelberger, L. & Rothman, S., 868.
Cram, E. B., 912.
—— & Figgat, W. B., 915.
—— & Files, V. S., 914.
——, —— & Jones, M. F., 913.
Cross, F. W., 928.
Crowther, A. F., Curd, F. H. S. & Rose, F. L., (866).
Curd, F. H. S., Graham, W. & Rose, F. L., (866).
Cuthbertson, W. W. & Moffatt, J. S., (866).

Darío Fábrega, R., (906).
Davis, D. E., 888.
De, M. N. & Datta, P. N., 862.
Dias, E., Laranja, F. S. & Nobrega, G., (881).
Downing, J. G., (911).
Dulaney, A. D., with Priest, J. B., Almeda, M. L. & Parker, B., 857.
Durieux, C., Trenous, J. & Tanguy, F., 905.

El Ghaffar, Y. A., 905.
El-Ramli, A. H., 900.
Eyles, D. E. & Young, M. D., 859.

Faust, E. C., Lewis, R., Heilbrunn, I., Hickman, M. L. M. & Everritt, M. G., 902.
Fernandez, J. M. M. & Bergel, M., 911.
Ferro-Luzzi, G., 931.
Field, J. W., 861.
Fox, J. P., 889.

Gall, D., 936.
Gaud, J. & Maurice, A., 912.
Geigy, R., 873.
Gelfand, M., 913.
Ghosal, S. M. & Sinha, Y. K., 882.
Ghosh, B. N., 862.
Giroud, P. & Ciaccio, G., 885.
Gohar, M. A., 901.
——, Elyan, A., Makkawi, M., Eissa, A. & Bashatly, A., 897.
Goodman, L., 910.
Groenendijk, H. J., (885).

Hadjinikolau, J. & Busvine, J. R., 936.
Hauschka, T. & Goodwin, M. B., (881).
Haworth, R. D. & Robinson, S., (866).
Hertig, M. & Fairchild, G. B., 884.
Hill, K. R., 874.

Ibrahim, M., Sorour, A. & El-Sherif, A., 914.
d'Ignazio, C., (858), 888.
Irvin, J. L. & Irvin, E. M., (866) *bis*.

Jackson, C. H. N., 874.
Jafar, M., 862.
Jeffery, G. & Oliver-Gonzalez, J., (923).
Jones, M. F. & Brady, F. J., 916, 918.
—— & Hummel, M. S., 919.
——, Newton, W. L., Weibel, S. R., Warren, H. B., Steinle, M. L. & Figgat, W. B., 917.
J. National Malaria Soc., (856), (871).

Klatskin, G. & Friedman, H., 904.
Kordi, A. H., 901.
Kuehl, F. A., Jr., Spencer, C. F. & Folkers, K., (866).

Laemmert, H. W., Jr., 894.
Laird, M., (933).
Lamy, L. & Chevrier, A. M., Mlle., 904.
Launoy, L. & Chaboud, G., Mlle., 879.
—— & Jeanpierre, C., 879 *bis*.
Le Gac, P., 921.
Lengrand, J., (891).
Liebow, A. A., Milliken, N. T. & Hannum, C. A., 908.
Lomax, P. H., 862.

McCulloch, R. N. & Waterhouse, D. F., 869.
McDaniel, G. E. & Hemphill, F. M., 856.
Macfie, J. W. S., 933.
McMullen, D. B. & Brackett, S., 920.
Maier, J., 867.
——, Bang, F. B. & Hairston, N. G., 860.
Martinez Dominguez, V., (911).
Mazzotti, L., 922.
Mégroz, R. L., (937).
Melnick, J. L. & Paul, J. R., 895.
Meyer, K. F. & Foster, L. E., 896.
Mohapatra, G. S., 907.
Morgan, H. R., Neva, F. A., Fahey, R. J. & Finland, M., 887.
Mukherjee, N. N., 909.

Nabarro, J. D. N., (930).
Neri, I., 933.
Nolan, M. O., Mann, E. R. & Churchill, H. M 919.
Noury, M., 889.
Noyan, A., 855.

Ottolina, C., 915.

Paranjothy, J. T., 860.
Parekh, J. H. & Boghani, B. P., 862.
Patton, R. L. & Sarkaria, D. S., (936).
Payzin, S. & Golem, S. B., 891.
Pullman, T. N., Alving, A. S., Jones, R., Jr., Whorton, C. M., Craige, B., Jr. & Eichelberger, L., 865.

[continued overleaf

ALPHABETICAL LIST OF AUTHORS OR SOURCES—*cont. from page 3*

Ranque, J., Ranque, M., Cabassu, J. & Cabassu, H., 883.
Rao, S. R., 896.
Rau, L., 858.
Rawson, A. J., Collins, L. H., Jr. & Grant, J. L., 929.
Rens, M. R., 909.
de Reyes Pugnaire, M., 922.
Ricketts, W. E., 893.
van Riel, J., (866).
de Rodaniche, E. C. & Rodaniche, A., (892).
Rodhain, J. & van Hoop, M. T., (907).
Romaña, C., (881).
Rosove, L., West, H. E. & Bower, A. G., 892.
Russo, E. & Gomes, R. P., 930.

Safwat, Y. & Adham, I., 898, 899.
Saleun, G. & Chassain, J., 875, 878.
Sarrouy, C., Prost & Cabannes, (858).
Sautet, J., Ranque, J., Vuillet, F. & Vuillet, J., 856.
Savoor, S. R., Soman, D. W. & Vahia, N. S., 888.
——, Vahia, N. S. & Soman, D. W., 888.
Schmieder, F., 887.
Schneider, J., Dignat, M., Voron & Sfar, M., 868.
——, Larabi, M. & Balti, M., 868.
—— & Méchali, D., 865.
Scholten, C., (912).
Schujman, S., (911).
Seaman, G. R., 932.
Sen Gupta, P. C., 881.
——, Mallik, K. N. B. & Chakravarty, N. K., 882.
Sergent, Edm. & Sergent, Et., 937.
Sforza, M., 887, 890.
—— & Solinas, N., 890.
Shortt, H. E. & Garnham, P. C. C., 872.
Sicé, A., 876.
Simpson, M. L., 873.
Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. G., Beard, R. R. & Saito, M. T., 929.
Soman, D. W. & Das Menon, V. K. 890.
Spies, T. D., Garcia Lopez, G., Milanes, F., Lopez Toca, R. & Culver, B., 928.
Spitler, D. K., 860.
Srivastava, R. S., 862.
Stewart, W., 930.
Stoll, N. R., (921).
Stowe, M., (927).
Streeton, G. E. W., Cohen, R. S., Gutteridge, N. M., Wilmer, N. B., Brown, H. E., Smith, D. J. W. & Derrick, E. H., 891.

Tanguy, F., Robin, C. & Raoult, A., 905.
Tedeschi, G. G., 932.
Tetzlaff, F., 871.
Teuber, F., (896).
Theiler, G., (935).
Theodor, O., 934.
Thiodet, J., (921).
Tiner, J. D. & Chin, T. H., (921).
Tobie, E. J. & Rees, C. W., 880.
Trinquier, E. & Ceccaldi, J., 928.
—— & Pellissier, A., 877 *bis*.
Trowell, H. C., 925.

Valentine, W. N. & Neel, J. V., 927.
Vaughan-Jones, T. G. C., 879.
Veeraraghavan, N., 855.
Vuillet, J. & Levavasseur, G., 857.

Waddell, M. B. & Kumm, H. W., 894.
Wadsworth, G. R., (906).
Ward, P. A., Travis, D. & Rue, R. E., 915 *bis*.
Watson, J., with Stahman, A. W. & Bilello, F. P., 926.
Whitman, L., 872.
Williams, A. A., (921).
Wills, L., 924.
Worth, H. I., 937.
Wright, W. H., 913.

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